REVIEW ARTICLE

Holistic approach to opioid use disorder: Think nitric oxide!

Marvin A. Sackner, MD; Jose R. Lopez, MD; Veronica Banderas, BA TR; Jose A. Adams, MD

ARTICLE INFO

Keywords:
pain
opioid addiction
nitric oxide
α2 adrenoceptor agonists

DOI:10.5055/jom.2019.0543

ABSTRACT

This review deals with opioid addiction, chronic pain, and an innovative, noninvasive technology with simultaneous, beneficial applications for both conditions. This technology, called passive simulated jogging device (GENTLE JOGGER, JD) targets addiction and pain by increasing endothelial nitric oxide (NO) bioavailability. It can be self-administered while sitting or lying without resorting to multitasking thereby allowing watching television or operating a computer while effortless, physical activity is produced from motorized foot pedals repetitively striking a bumper at 175-190 times per minute which adds small pulses to the circulation. This action increases shear stress (friction) to vascular endothelium that stimulates endothelial nitric oxide synthase (eNOS) to increase NO that decreases oxidative stress and inflammation, and, slows accelerated vascular ageing associated with opioids.

Since the 1970s, clonidine, lofexidine, and dexmedetomidine have been used off-label to suppress opioid withdrawal symptoms precipitated by excessive release of norepinephrine. These pharmacotherapy aids to withdrawal and tapering opioid dosagadrenoceptor agonists that act through eNOS to inhibit norepinephrine. Increasing NO as with JD and/ or in conjunction with opioid agonists should help stabilization, tapering, withdrawal, and relapses stages of addiction. Nitric oxide as increased with JD technology is antinociceptive as demonstrated in chronic and subacute pain states, viz., fibromyalgia, osteoarthritis, peripheral arterial disease, delayed onset of muscle soreness (DOMS), and sickle cell disease. Jogging device decreases elevated blood pressure that is produced with physical inactivity, a risk to opioid use disorder (OUD). Thus, JD provides holistic, cost-effective approach to opioid addiction as well as chronic and subacute pain.

INTRODUCTION

Addiction to opioids is a growing, deadly, health issue in the United States and worldwide. Opioids derived from the poppy plant include (1) opium, morphine, and codeine, (2) synthesized by pharmaceutical companies such as fentanyl and oxycontin, and (3) manufactured by independent, unregulated drug laboratories such as heroin. Legal opioids are prescribed to control pain, diminish cough, and relieve diarrhea. Nontherapeutic, illicit opioids are taken to produce pain relief, euphoria, tranquility, sedation, and pleasure. In high dosage, both legal and illicit opioids have potential to suppress activity of the respiratory center potentially causing respiratory arrest and ultimately death.[1-6] Surprisingly, there are a paucity of peer-reviewed papers on health-related quality of life (QoL) in patients receiving long-term medical opioid therapy for relief of pain.[7-10] The need to assess gaps in our knowledge regarding dangers of opioids to health as well as new, nonpharmacological methods of

controlling both pain and addiction are obvious. This review deals with significant and missing knowledge of opioid use disorder (OUD), addiction, and chronic pain as well as the characterization of a new, innovative, noninvasive device that increases release of endothelial NO into the circulation to favorably affect both issues.

OPIOID ADDICTION

Opioid-addiction occurs in individuals from every educational and socioeconomic background. Recognition of this healthcare crisis has promoted a change of physicians' prescribing practices as well as a priority to train first responders in parenteral administration of naloxone, an antagonist to opioid-related respiratory center depression. In the United States, an estimated 400,000 persons have used heroin in the past month, and 4 million have reported nonmedical use of prescription pain relievers. In drug overdose hospitalizations, 16 percent were associated with prescription opioid overdose and 2 percent with heroin overdose. In terms of prevalence of cardiac arrest, heroin overdose was the most common opioid, followed by prescription opioids and least common by nonopioid opioids. Further, the rate of cardiac arrest has become increasing disproportionate in patients with opioid overdoses.[11] In 2016, opioid prescriptions accounted for 40,000 deaths, half from fentanyl; drug poisoning is one of the leading causes of accidental death in the United States. In a recent paper, the annual number of opioid overdose deaths is projected to increase from 33,100 in 2015 to 81,700 in 2025, a 147 percent increase from 2015. From 2016 to 2025, 700,400 Americans are projected to die from opioid overdose, with 80 percent of the deaths attributable to illicit opioids.[12] The number of individuals using illicit opioids is projected to increase by 61 percent—from 0.93 million in 2015 to 1.50 million by 2025. Lowering prescription opioid misuse from 2015 levels has been projected to decrease overdose deaths by only 3.0 percent to 5.3 percent.[12] Therefore, attention to illicit OUD must be a top priority to control the opioid epidemic.

In 2017, the odds of death for heart disease were one in six, cancer one in seven, suicide one in 88, opioid overdose one in 96, and motor vehicle crash 1 in 96. Approximately 3 million persons in the United States and almost 16 million worldwide have a current or past OUD.[12] The global burden of opioid-related conditions approaches 11 million life-years lost from health problems, disabilities, and early death.[5,13,14] Despite governmental allocation of extensive financial resources to stem the tide of opioid addiction, a positive solution has not been at hand. This might relate in part to the major emphasis on pharmacotherapy, eg, administration of diminishing dosages of substitute opioid with less rewarding drugs (methadone, buprenorphine, and naltrexone) and far less attention to treatment of mental and physical contributing factors to addiction.

UNINTENDED CONSEQUENCES OF INCREASING OPIOID AVAILABILITY

Pain relieving narcotics have been available for hundreds of years, but addiction remained at low, manageable levels until the 1990s when two major developments occurred that focused on "inadequate" opioid dosing. The first was mainly a result of massive and unintended consequences of increasing opioid availability that is not well explained. "Educational" campaigns by a pharmaceutical company that marketed a new, enormously popular extended-release analgesic, created an intense focus on pain treatment in medical circles. In 1995, the president of a major scientific organization indicated that pain should be considered the "fifth vital sign." This view was accepted by a nationally recognized nonprofit health standards setting and accrediting body, the Joint Commission on the Accreditation of Healthcare Organizations which released a scathing report on the undertreatment of pain in the United States. The report concluded (subsequently rejected in 2016) that effective narcotic analgesics were available but seldom used, and that doctors were ignoring pain management because of an irrational fear of addiction. It was argued by some that narcotics should be more widely used (later recognized as incorrect!) by appropriate clinical use that rarely generated addictive behaviors. Time magazine featured this report on its cover, characterizing it as a national scandal given that most physicians were unaware about appropriate pain management, particularly the role of opioid analgesics.[2,14] The highly successful marketing campaign prompted doctors to often inappropriately prescribe narcotics in record numbers.

The second major development leading to prescription opioid abuse was the introduction of a sustained-release drug, oxycodone, that provided pain relief for 8 to 12 h. With this new formulation, oxycodone (OxyContin®), an excellent pain reliever but also a

powerful euphorigenic agent needed to be taken only once or twice a day, instead of every 2 to 4 h. The extended-release capsules contained a built-in delivery system that released the drug slowly over time from a large self-contained reservoir of the active drug moiety. The Food and Drug Administration (FDA), concluded that the delay in reinforcement imposed by slow release of oxycodone would dissuade abuse because to reinforce a behavior such as drug seeking, an immediate reward was necessary. Addicts quickly realized that they could subvert the slow-release device by crushing or dissolving the pills, making large amounts of oxycodone immediately available in a form suitable for snorting or intravenous injection.

Compared with a standard immediate-release tablet that typically contained 5 mg of active drug, the new extended release version of oxycodone could easily hold 80 mg or 14 times as much as a single tablet, making one dose go a very long way. Simple breaching of the reservoir allowed access to this enormous supply of this opioid. Further, the tablet contained large amounts of pure oxycodone, quite unlike most immediate-release compounds that were mixed with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), which most addicts were hesitant to use because of health considerations (eg, gastric bleeds or liver damage) and/or the irritation to the nasal passage and pain at the injection site in individuals for whom such routes of administration were desirable.

Oxycodone, an effective analgesic, became a highly prized drug for abuse.[1] Aside from whatever rewarding sensations that led to repetitive use, several factors favored prescription opioids in a new set of drug users. Oxycodone produced a good, dependable, "safe" high because unlike heroin, the dose was known with certainty and was clearly labeled. Therefore, addicts considered that danger to overdose was greatly reduced.

Moreover, since this opioid was an FDA-approved drug, they erroneously believed that its possession might lead to fewer legal problems.[11]

ONSET OF LONG–TERM RELIANCE ON OPIOIDS

The elapsed time between the first oral exposure to opioids and habituation/addiction to daily opioid intake is surprisingly short. For oral opioids, daily use over 90 days produces a high prevalence of sustained use.[13-15] Daily administration of oral morphine for 30 days in ten patients with low back pain compared to a placebo group using MRI assessment found significant volumetric reduction of gray matter in several brain regions.[16]

For daily intravenous heroin injections, addiction could be as brief as 1-3 weeks.[17] These individuals are at high risk to overdosage and death. More than three out of five drug overdose deaths involve opioids that act on the peripheral nervous system or specific receptors in the brain to reduce pain intensity, but continual use leads to drug tolerance and ineffectiveness. Overdose deaths from opioids have increased by more than five times since 1999. Opioid overdoses killed at least 42,000 Americans in 2016 of which about 40 percent were from previous or currently prescribed opioids. According to the Centers for Disease Control and Prevention, more than 140 Americans died per day from drug overdoses with 91 deaths per day specifically due to opioids. Over 52,404 Americans died from drug overdoses in 2015. In the United States, deaths due to suicide and unintentional overdose pose a growing, public health issue. Combined deaths among Americans from suicide and unintentional overdose increased from 41,000 in 2000 to 111,749 in 2017 and have exceeded deaths from diabetes since 2010. Interventions that address the shared causes and risk factors of suicide and unintentional overdose such as improvement of quality of pain care, access to psychotherapy, and medication-assisted treatment (MAT) for OUDs, to simultaneously address both problems have been insufficient.[18]

Substance misuse often begins during adolescence with over 80 percent of drug abusers taking drugs during adolescence. Only about 11 percent of individuals ages 12 and older and only about 6 percent of adolescents 12-17 years old who need treatment for substance abuse receive it.

Furthermore, over half of the adolescents receiving treatment will relapse within one year of treatment, suggesting that more accessible and effective programs are needed to prevent and treat substance use in adolescents.[19] Moreover, adolescents who reported nonmedical use of prescription opioids (NMUPO) for pain relief involving opioid analgesics with high misuse potential, or multiple prescription opioids had significantly greater odds of substance use disorder (SUD) symptoms at age 35, relative to those who had no history of NMUPO during adolescence. In addition, medical use of prescription opioids after initiating NMUPO (or NMUPO only) during adolescence was associated

with significantly greater odds of subsequent symptoms of SUD at age 35 relative to those who reported the medical use of prescription opioids only or had no medical use or NMUPO during adolescence.[20] Thus, prevention of OUD in adults must take into consideration that opioids for pain relief is a risk in youths to later life.

MEDICAL PREVENTION OF OPIOID USE DISORDER

Prevention relies on public and prescriber education, prescription drug monitoring programs, and safe medication disposal. Education of opioid overdose and naloxone, an injectable, antagonist to opioid respiratory depression as a rescue medication, and training to first responders, has great promise. From the start of the current opioid epidemic to the present, there has been overprescribing of opioids related to the following considerations: (1) inadequate training in pain and addiction medicine, (2) societal medication mania for fast pain relief, (3) patients as well as their families demanding "shots," (4) intensive marketing of opioids by the pharmaceutical industry, (5) eagerness by healthcare workers to relieve pain and suffering, (6) insufficient numbers of pain specialists offering comprehensive pain management, and (7) a reimbursement system that solely favors drug usage for pain management.[21] However, outcomes from clinical trials dealing with prevention of opioid addiction are sorely lacking.

PHARMACOTHERAPY AND COUNSELING FOR OPIOID ADDICTION

In the long-term, OUD may evolve into illegal taking of opioids by intravenous injection, chewing tablets, or nasal insufflation for rapid onset of action thereby providing greater perceived pleasure. Such individuals frequently may be unemployed, homeless, and/or involved in drug-related criminal activities, but are increasingly found in suburban America. Costs to society for medical care, lost productivity, crime, and social welfare of these individuals are estimated to be in the billions of dollars. The treatment of addiction dependence using agonist substitution, such as methadone, has been shown to be safe and effective since the late 1960s.

Methadone maintenance therapy (MMT), and more recently other opioid agonists such as buprenorphine and an opioid antagonist such as naltrexone, have potential for relieving craving, suppressing withdrawal symptoms, and blocking opioid euphoria. While some opioid agonist taking patients have reductions in HIV-risk behaviors as well as improved social integration and psychosocial functioning, many continue to suffer from a variety of psychiatric and medical ailments, including hepatitis, HIV, major depression, other substance abuse disorders, and poor QoL.[22]

The National Drug Abuse Treatment Clinical Trials Network summarized the multisite Prescription Opioid Addiction Treatment Study (POATS), the largest clinical trial conducted in prescription opioids dependent patients (N = 653). Combinations of buprenorphine-naloxone therapy of varying duration and intensity as well as counseling were analyzed.

Primary outcome analysis revealed no overall benefit to adding drug counseling to buprenorphine-naloxone and weekly medical management. Only 7 percent of patients achieved a successful outcome (abstinence or near-abstinence from opioids) during a 4-week taper and 8-week follow-up. Patients receiving opioid agonist treatment at the time of follow-up were more likely to have better outcomes than those with drug counseling though a number succeeded without agonist treatment. Some patients on this program initiated risky use patterns including heroin injections. The main limitation of POATS was the low success of long-term follow-up.[23] The limited success of POATS suggests an individualized approach to behavioral interventions as relates to pharmacotherapy. Since some heroin abusers benefit from counseling, they might do well with just medical management while others should receive additional counseling. Because POATS also found that opioid use during the first two weeks of buprenorphine-naloxone treatment was associated with a poor prognosis, patients who do not stabilize within two weeks could be offered more intensive, individualized care.[24]

POOR QUALITY OF LIFE

In general, scant attention has been paid to improve the poor QoL in patients receiving long-term opioid therapy in terms of physical inactivity, depression, suicidal tendencies, dissatisfaction with one's physical self, and some element of social isolation, considerations that are not unique to opioid addiction. Not only do these features highlight the importance of addressing mental health and of

providing support for physical and social well-being during treatment, but they also serve as a reminder that opioid-addicted individuals are vulnerable to many of the same situations and conditions as those without it.[25] To put this into perspective, a five year follow-up after the start of methadone treatment in 159 opioid-dependent individuals found that low QoL scores were present on various domains.[7-10] Severity of psychological distress and taking medication for psychological problems as well as the inability to change one's living situation were associated with lower QoL. The latter, points out need for a holistic approach for treatment and support beyond fixing the negative physical aspects of opioid addiction.[26] Here, attention should be directed to correction of insufficient pain management and depression that contribute to lower QoL among individuals with chronic pain and OUD.[27] Since such individuals have a high probability of being unemployed, efforts should be made to return then to the workforce.

PHYSICAL ACTIVITY IN OPIOID USE DISORDER

Physical activity is any bodily movement produced by skeletal muscles that increases energy expenditure as measured by oxygen consumption. It includes working, playing, carrying out household chores, traveling, and engaging in recreational pursuits. The term "physical activity" should be differentiated from "exercise," a subcategory of physical activity which is planned, structured, repetitive, with an aim to improve or maintain one or more components of physical fitness. Physical inactivity and failure to meet exercise recommendations of the American Heart Association (AHA) are independent risks to health but only recently have their differences been clarified. Most reports equate inadequate exercise to ill cardiovascular health effects as less than 30 min daily of brisk walking or slow jogging at least five days per week. But compliance with such guidelines while sitting and watching a computer screen or television program over a much longer uninterrupted time period negates the beneficial effects of short exercise duration on vascular health. The average American adult sits about 12 h per day watching television, operating a computer, in a transportation vehicle, and in a chair while eating. Reducing physical inactivity time is a more important factor to good health than following recommended exercise protocols owing to the greater allocation of time between the two.[28-32] Moreover, an EEG study indicated that avoiding sedentary behaviors requires more cortical brain resources than avoiding physical activity.[33] Although preclinical animal studies suggest that physical activity protects against opioid abuse vulnerability, no such evidence has yet been obtained in human studies.[34]

In methadone-treated opioid users, time spent sitting was significantly and positively associated with depression after controlling for physical functioning, physical activity level, and other health-related factors. This finding is consistent with previous studies that have linked sedentary behavior or physical inactivity as prolonged periods of uninterrupted sitting to increased risk of depression.[22] As a component of the treatment for OUD, effective means to limit physical inactivity must be utilized.

In a meta-analysis of 22 SUDs that included three types of addictive substances, alcohol, nicotine, and opioids, physical activity had the most persistent, long lasting effects on abstinence, possibly related to its role in increasing brain-derived neurotrophic factor (BDNF) and glial, cell line-derived neurotrophic factor (GDNF), reparative neurological factors. These factors aid survival and function of adult neurons, learning and memory and synaptic plasticity. In rodent studies, the question as to whether BDNF or GDNF facilitates or inhibits drug-taking behaviors is dependent on the drug type, brain site, the addiction phase (initiation, maintenance, or abstinence/relapse), the time interval between site specific BDNF or GDNF injections into the brain and reward- and relapse-related behavioral assessments.[35]

Physical activity/exercise might ease withdrawal symptoms, depression, and anxiety but there have not been any well-controlled clinical trials published to confirm this assertion. In fact, there are no rigorous clinical trials varying intensity, duration, and frequency of physical activity/exercise and/or limitation of physical inactivity reported in opioid addicts. In the 2014 Behavioral Risk Factor Surveillance System (BRFSS) of the general population, 27.5 percent of adults aged ≥50 years reported no physical activity outside of work during the previous month. Prevalence of physical inactivity significantly increased with increasing age and was 25 percent among adults aged 50-64 years, 27 percent among those aged 65-74 years, and 35 percent among those aged ≥75 years. Inactivity was significantly higher among women than men and prevalence significantly

increased with decreasing levels of education and increasing body mass index.[32]

Reviewer in a group of 305 methadone-maintained smokers, only 38 percent of participants met weekly recommendations for physical activity and nearly 25 percent reported no physical activity. Those who did not meet recommended exercise guidelines were significantly more likely to relapse.[36] Poor adherence to exercise guidelines by opioid abusers prevents recommending exercise as a reliable first-line therapy.

ADHERENCE TO THERAPY

Approximately 50 percent of opioid-addicted patients fail to take 90 percent of prescribed anti-opioid addiction medications but convincing statistics on this point are unavailable. The reasons for nonadherence include: (1) uncertainty regarding medication effectiveness, (2) lack of understanding of need for consistent dosing and following treatment recommendations, (3) complexity of the regimen, (4) side effects or anticipation of side effects, (5) psychiatric comorbidity (specifically depression), (6) desire to get "high" from medication, (7) impatience waiting for medication to work, (8) denial of existence or severity of illness, (9) perceived stigma, (10) reluctance to mix medication with alcohol or drugs, (11) medication-induced interference with or blockade of drug "high."[36] In about 3,000 patients reviewed for adherence to medications by insurance claims who were treated with buprenorphine for opioid dependence, 22 percent had concomitant anxiety disorder, 16 percent major depressive/bipolar disorder, and 32 percent mental health disorder. Patients diagnosed with major depressive/bipolar disorder were significantly less likely to adhere to buprenorphine therapy than patients without it, thereby indicating that a psychiatric comorbidity can negatively affect adherence.[37] Thus, clinicians treating OUD with buprenorphine need to screen for psychiatric disorders and monitor medication adherence. New technology and drugs to curb opioid dependence must consider nonadherence to therapy in their trial design.

Super-utilizers, individuals who fill more than four opioid medications in a 6-month period, are at higher risk for nonadherence to medications prescribed for chronic diseases. Given the magnitude and clinical importance of medication nonadherence in this population, this unwanted consequence of heavy utilization of opioids warrants a more collaborative and holistic approach to this high risk population.[38]

PAIN AND ADDICTION

Chronic pain, one of the common reasons that adults seek medical care, has been linked to restrictions in mobility and daily activities, dependence on opioids, anxiety and depression, and poor perceived health or reduced QoL. High-impact chronic pain is characterized by limitation of life or work activities. An estimated 50-100 million US adults have chronic pain and 20 million US adults have high-impact chronic pain, with higher prevalence among women, older adults, previously but not currently employed adults, adults living in poverty, adults with public health insurance, and rural residents as well as those with lower levels of education and among adults with private health insurance.[39,40]

Treating "pain and addiction" as two separate issues generally leads to unsuccessful outcomes for both issues. Patients with pain and addiction often have multiple psychological, psychiatric, and medical comorbidities with associated poly-pharmaceuticals, all interacting with each other in complex ways. The latter is the key driver of evolution of acute pain to severely disabling chronic pain and associated adverse outcomes, rather than the persistence of injuries. Chronic pain contributes to an estimated $560 billion each year in direct medical costs, lost productivity, and disability programs.[41] Among those individuals with both pain and addiction, opioid abuse precedes pain in 58 percent while pain precedes addiction in 35 percent; therefore, both situations need to be therapeutically addressed nearly at the same time to achieve successful outcomes.[41]

Psychosocial interventions for opioid addiction alone generally fail to reverse addiction. Whether compelled or voluntary, return to opioid use approaches 80 percent within two years of intensive residential treatment. For treatment of opioid addiction, there is little consensus for which psychosocial treatments work best in conjunction with FDA-approved drugs, eg, methadone, buprenorphine, naltrexone, and lofexidine. For medications alone, clinical experience is the longest for methadone which has the greatest body of research supporting its utilization. Buprenorphine has a similar mechanism of action compared to methadone (partial versus full

agonist). Like other opioid agonists, these two drugs have potential to induce lethal suppression of respiration when given in doses that exceed an individual's tolerance. Naltrexone, an opiate antagonist that seems to reduce craving, has less of an historical basis for effectiveness. Each of the three available FDA approved medications to treat opioid addiction show superior treatment outcomes to nondrug-based treatments. Increased retention reduces mortality, improves social function, and is associated with decreased drug use and improved QoL.[42,43] However, there does not appear to be any rigorous, designed peer-reviewed publications of large population studies with several years of follow-up to support the preceding claim. Of interest, in 2018, FDA-approved lofexidine, an alpha2-α agonist for up to 14 days use to decrease the characteristic symptoms of opioid withdrawal.[44]

PHYSICAL ACTIVITY AND EXERCISE FOR CHRONIC PAIN

Physical activity generally improves pain sensation and related symptoms. Strict guidelines for implementing physical activity are lacking for chronic pain but frequent body movements are preferable to none. Moderate to strong evidence suggests that movements and psychosocial interventions are effective for relieving pain and improving function for musculoskeletal pain. NSAIDs and opioids reduce pain in the short-term, but the effect size is modest and potential for adverse effects require caution.[40,45] During and after exercise, different endogenous systems are activated, which release substances or neurotransmitters, such as opioids, NO, serotonin, catecholamines, and endocannabinoids that may modulate pain perception.[46] A sedentary lifestyle contributes wholly or partially to chronic pain.[47] The innovative, passive-simulated jogging device (JD) described below directly addresses the health hazard of a sedentary lifestyle through increasing bioavailability of NO with relief of chronic pain and acute lowering blood pressure.[48-50]

WELLNESS TECHNOLOGIES

Our holistic approach to both OUD and chronic pain has its basis in selectively promoting increased physical activity on the one hand and decreasing physical inactivity on the other. With regards to achieving abstinence and reducing opioid addiction relapses, exercise strategies have not been effectively reported, but such trials have not been adequately designed as to frequency, duration, and intensity. Therefore, the place of exercise as a therapeutic modality in OUD remains an open question. As to exercise improving mood, QoL, and reduction of substance abuse, assertions have been anecdotal and not definitive.[51,52]

Poor adherence to recommendations for increased physical activity and/ or decreased physical inactivity minimize their benefits from being realized in individuals with OUD which is also true for normal populations as well as patients with heart failure, coronary artery disease, cancers, obesity, fibromyalgia, substance abuse disorders, and hypertension among others. Group exercise programs and monetary rewards have been advocated to improve adherence for substance abuse users, but these enticements have not made a major impact on adherence. A commonly cited statistic is that approximately 50 percent of individuals dropout within six months of initiation of exercise programs, an insufficient time duration to garner its benefits.[53]

The major physiological basis for achieving wellness is enhancing bioavailability of endothelial-generated nitric oxide (eNO) through increased shear stress to the vascular endothelium produced by physical activity. Since insufficient physical activity is present in the majority of adults, there is need for technologies to replicate its benefits that require minimal or no effort and limited behavioral change. Such technologies, the motion platform and passive simulated JD which will be described below have major applications for a healthy life as well as a positive impact on the current worldwide epidemic of opioid addiction, the main subject of this review. The important health benefits of NO are summarized in Table 1.

MOTION PLATFORM FOR INCREASING ENDOTHELIAL SHEAR STRESS

Exercise and physical activity benefit health by increasing bioavailability of NO and upregulating antioxidant anti-inflammatory defenses as a result of increased shear stress (friction) to the vascular endothelium. Owing to the poor adherence of individuals worldwide to exercise and physical activity, this consideration prompted us to design a motion platform that effortlessly produced whole-body periodic acceleration (WBPA) as a means of increasing pulsatile shear stress to the endothelium. This

Table 1. Actions of NO released from eNOS activity

Action	Effects
Vasodilator	Acts on vascular smooth muscle to increase cGMP, beneficial in peripheral vascular disease, improves CFR
Reduces blood pressure	Treats systemic and pulmonary hypertension
Anti-atherosclerotic	Prevents adhesion of leukocytes and platelets to endothelium leading to endothelial dysfunction
Aids calcium egress from contracted muscle cells	Hastens recovery of DOMS, improves Duchenne muscular dystrophy
Anti-inflammation	Inhibits activity of NF-κβ, IL-1β, IL-6, IL-8, IL-18, TNF-α
Reduces oxidative stress	Scavenges ROS and RNS
Antinociception	PeripheraI: inhibits NF-κβ and endothelin-1; Central: during physical activity
Anti-tumorigenic	Inhibits NF-κß and PARP-1, factors left unchecked prevent programmed cell death (apoptosis) of tumor cells
Organ preconditioning and postconditioning	Minimizes deleterious effects of I/R injury to heart, brain, gut, lungs, liver, kidneys, and skeletal muscles by suppressing NF-κβ and reducing oxidative stress
Antidiabetogenic	Combats microvascular complications of diabetes and reduces insulin resistance
Signals upregulation BDNF, GDNF, and SIRT1	Strengthens memory and provides neuroprotection & neurorepair
Minimizes cognitive decline with ageing	Increases microvascular cerebral blood flow
Stroke protection	Increases microvascular cerebral blood flow
Promotes reverse ventricular remodeling	Improves ventricular function post myocardial infarction and in ischemic and non-ischemic heart disease
Activates telomerase	Delays endothelial cell senescence and is thereby is anti-ageing
Benefits sickle cell disease	Potential to prevent and ameliorate vaso-occlusive pain crisis in home or hospital environments
Increases angiogenesis	Promotes wound and fracture healing
Inhibits norepinephrine activity	Relieves symptoms of opioid withdrawal & aids in tapering opioid dosing

device consisted of a horizontal, motorized platform with a gurney-like appearance that added pulses as a function of platform frequency to the circulation by passively administering repetitive, sinusoidal, rapid head-to-foot platform movements to supine subjects (ExerRest®, NIMS, Miami, FL 33137). It was based on the pioneering, perfused, isolated, blood vessel experiments in 1991 of Hutcheson and Griffith.[54] With a pump that delivered pulsatile flow of a physiological solution, they found that NO was released from the endothelium of a perfused blood vessel with peak release occurring between 250 and 360 pulses per minute. Our laboratory confirmed their observations of a dose response between NO release and number of pulses in a perfused blood vessel. We utilized an isolated porcine aorta perfused with a physiological solution of (1) non-pulsatile flow, (2) pulsatile flow at one pulse per minute, and (3) pulsatile flow superimposed with added pulses from a motion platform moving at 180 times per minute. With pulsatile flow, NO increased about 300 percent above steady flow and further increased with added pulses, due to fluid inertia, from the motion platform about 1000 percent over steady flow. In intact, anesthetized pigs, application of the motion platform produced significant

decreases of mean femoral blood pressure from 93±6 mmHg to 80±5 mmHg and pulmonary artery pressure from 12±1 mmHg to 9.5±1 mmHg demonstrating the vasodilator properties of pulsatile shear stress to the endothelium that related mainly to increased NO bioavailability.[55]

Preclinical investigations of WBPA have been accomplished with structural modifications of the human designed, motion platform that demonstrated beneficial effects in experimental systemic and pulmonary arterial hypertension, asthma, meconium aspiration, pre- and postconditioning in ischemia reperfusion injury, regional microvascular blood flows, sepsis, hemorrhagic shock, experimental stroke, experimental myocardial infarction, cardiopulmonary resuscitation, mice model of muscular dystrophy, oxidative stress, limb ischemia, eccentric exercise, and formation of cerebral neurotrophic factors. The motion platform increased bioavailability of NO, prostacyclin, tissue plasminogen activator (tPA) and adrenomedullin as well as upregulated total antioxidant capacity through increased pulsatile shear stress to the endothelium.[55-71] Further, human investigations showed that WBPA increased NO bioavailability at rest and exercise, produced brachial flow-mediated vasodilatation and increased coronary flow reserve (CFR), hastened recovery of strength from delayed onset of muscle soreness (DOMS) due to eccentric exercise, improved symptoms of fibromyalgia including pain, increased walking distance in peripheral vascular disease, and increased exercise capability in mild heart failure.[48,71-80]

An unpublished study from our laboratory in mice treated 1 h daily with WBPA on a motion platform for 2 weeks upregulated SIRT1, an anti-ageing molecule, amounting to ~148 percent in the brain, in skeletal muscle ~20 percent, and in heart ~31 percent. To put these results into perspective, laminar flow over an endothelial cell preparation for 16 h showed an increase of SIRT1 ~50 percent.[81]

For human applications, the motion platform was not widely adopted because it was too expensive, limited solely to use in the supine posture, and nonportable owing to its large footprint and weight (211 kg). It was registered as an FDA Class I (exempt) therapeutic vibrator with the following intended uses: "as an aid to temporarily increase local circulation, to provide temporary relief of minor aches and pains, and local muscle relaxation." Following a clinical trial for pain relief in fibromyalgia recommended by FDA, the motion platform was granted an expanded use, eg, "reducing morning stiffness."

PASSIVE SIMULATED JOGGING DEVICE

Because of its structural limitations as well as high price, the motion platform achieved limited acceptance in the marketplace. Therefore, a new wellness device was fabricated as a low cost, portable alternative, and patented as the passive simulated JD [GENTLE JOGGER]. This device, abbreviated JD, met FDA standards for low risk, wellness repetitive, alternating, movements of foot pedals placed within a chassis while the subject was seated or lying in a bed to produce effortless flexion and extension of the ankles such that soles of the feet tapped against a semi-rigid bumper as in locomotor activities.[82] JD weighed about 4.5 kg with chassis dimensions of 34 × 35 × 10 cm3 and was placed on the floor for seated and secured to the footplate of a bed for supine operation. Its foot pedals rapidly and repetitively alternate between right and left pedal movements to lift the forefeet upward about 2.5 cm followed by active downward tapping against a semi-rigid bumper placed within the chassis. In this manner, it simulated feet striking the ground during selective speeds of locomotor activities. Each time the passively moving foot pedals strike the bumper, a small pulse was transmitted from the feet to the circulation as a function of pedal speed. Buttons on the chassis control selection of speeds, viz, walk (~120 steps/min, jog ~150 steps/min, run ~175 steps/min and race ~190 steps/min) (Figures 1 and 2). Studies cited in this review were mostly done at "race" speed. An LED screen displays the number of steps and elapsed time of usage. An iPhone app connected to JD through blue tooth allowed speed control, measurement of foot weight on pedals for monitoring user compliance, and logging step count and duration of time used, eg, daily, weekly, and monthly. The JD produced the same effects as WBPA while transmitting pulses remote from tapping of the feet.[83]

The suggested usage duration of JD is 30 min, one to three times daily but longer durations such as approximately 1 h are safe, beneficial, and without deleterious effects. JD can be self-administered in home and workplace, to provide effortless physical activity without resort to multitasking. The dimensions are such that it can be operational underneath most desks and the forward passenger seat of commercial airlines or trains. During its operation, the upper extremities can freely move thereby allowing reading printed matter, writing, typing, eating, operating a computer, watching television, and lifting weights. Its intended uses comply with FDA suggestions for low

Figure 1. The feet are strapped to the pedals for firm coupling (straps not shown in image). Repetitively, the left pedal is elevated by the motor mechanism while the right pedal is depressed to tap against a fixed bumper within the chassis. This is followed by elevation of the right pedal and depression of the left pedal (not shown in figure).

Figure 2. This depicts the passive simulated JD applied in supine posture while the feet rest on the pedals. Its chassis is propped against the feet rail seen on the left side of the image. The chassis from is held in place during operation by a Velcro strap from the chassis to the feet rail (not shown in image). The feet are strapped to the pedals for firm coupling (straps not shown in image). The LED on top of the chassis displays number of steps (here seen as 382) as well as time of operation, and speed as walk, jog, race and run.

risk, noninvasive wellness devices (General Wellness: Policy for Low Risk Devices: Guidance for Industry and Food and Drug Administration Staff July 29, 2016). Clinical trials, though not required for FDA nonregulated wellness devices, have been completed in hypertension and heart disease to confirm FDA's suggested intended uses. A clinical trial using self-administered JD for prevention and treatment of type 2 diabetes in the home environment has been submitted for consideration of publication.[49,84]

A JD emulates voluntary physical activity since oxygen consumption increases during its operation.[85] Further, by increasing shear stress (friction) to the vascular endothelium through added pulses to the circulation, it increases NO bioavailability.[86,87] JD increases endogenous mediators, antioxidants, and, anti-inflammatory substances that can mitigate or improve risks associated with OUD.[65,66,88] Such risks include physical inactivity, endothelial dysfunction, oxidative stress, reduced cerebral neurotrophic factors, reduced cerebral blood flow, neuroinflammation, depression, anxiety, cognitive dysfunction, and premature mortality. JD incorporates objective means to assess adherence of use and provides a pleasurable tingling sensation of the lower extremities during usage. In conjunction with an iPhone app, "interval training programs" can be initiated with user selected timings that can prolong the tingling sensation throughout operation of JD such as repetitive intervals of 3 min of operation and 30 seconds of nonoperation, etc., over its total session duration.

PHARMACOTHERAPY FOR OPIOID USE DISORDER

Until recently, the FDA approved only three drugs for treatment of OUD, eg, methadone (opioid agonist), buprenorphine (partial opioid agonist), and naltrexone (opioid antagonist). MTT offered these drugs along with counseling and/or behavioral treatments in structured settings to prevent relapse after detoxification and stabilization. Despite methadone treatments beginning in the 1960s and more recently with other opioid agonist or antagonist substitution drugs, there is a dearth of long-term, rigorous controlled, treatment outcomes (> 1-5 years) in large populations of opioid abusers.

In 2018, FDA approved lofexidine for up to 14 days to lessen withdrawal symptoms during abrupt discontinuance of opioids. This drug, the first nonopioid treatment of opioid withdrawal symptoms approved by FDA, is an orally administered alpha 2-adrenoceptor agonist which reduces release of norepinephrine from the autonomic nervous system and brain. Elevated norepinephrine levels are responsible for opioid withdrawal symptoms of nausea, abdominal cramps, muscle spasm/twitching, aches and pains, runny eyes, and sleep disturbances among others.[44,89]

EXERCISE AS ADJUNCTIVE TREATMENT FOR OPIOID USE DISORDER

Exercise has been recommended as an adjunctive intervention for opioid agonist treatment owing to improving mood and overall QoL, and reducing substance abuse.

However, exercise for long-term OUD abstinence has not led to successful treatment outcomes. Failure has been attributed to poor adherence and dropout[52] but the poor rigor of exercise protocols with regards to frequency, duration, and intensity in published studies renders the role of exercise in OUD an open question.[23,52,53,90]

CONTRIBUTING FACTORS TO OPIOID ADDICTION

The factors that contribute to persistence of OUD and/or their side effects include among others (1) physical inactivity, (2) endothelial dysfunction, (3) arterial stiffness, (4) cognitive impairment, (5) oxidative stress, (6) neuroinflammation, (7) chronic pain, (8) depression, (9) anxiety, (10) craving, and (11) reward. In most instances, multiple factors coexist. For example, physical inactivity may produce oxidative stress, inflammation, chronic pain, and depression. Cognitive impairment may occur with combinations of physical inactivity, endothelial dysfunction, arterial stiffness, oxidative stress, and neuroinflammation.

PHYSICAL INACTIVITY

Guthold et al.[91] conducted a worldwide population-based analysis of self-reporting the prevalence of insufficient physical activity at the workplace, in the home, riding transportation vehicles, and during leisure time (ie, not doing at least 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity per week or any equivalent combination of the two). From 358 surveys of 168 countries that included 1.9 million participants, global age-standardized prevalence of insufficient physical activity was 27.5 percent. The investigators cautioned that if current trends continue, the 2025 global physical activity target of a 10 percent reduction of insufficient physical activity will not be met. Healthcare policies to increase levels of physical activity need to be prioritized and urgently scaled up because of the growing risks related to a sedentary lifestyle of hypertension, type 2 diabetes, depression, obesity, certain cancers, frailty, and premature death.[92,93] In waking hours, physical inactivity is mainly due to uninterrupted sitting while watching television or operating a personal computer. Overall, sitting by adults occupies approximately 12 h daily of waking hours. To overcome such inactivity, taking breaks from sitting every 20 min by arising from a chair and walking about for 2 min is effective but necessitates a behavioral change that has not yet been implemented in large population studies.[94,95] Alternately, an individual can remain seated during operation of JD as described in this review and still receive benefits of physical activity such as lowering blood pressure and diminishing glycemic rise caused by inactivity.[49] With regards to attributing physical inactivity as a risk factor in opioid addiction,[96] there has not yet been a published study as to whether addicted individuals are more physically inactive than nonaddicted individuals. However, physical inactivity among American adults is so ubiquitous that at the least it could be synergistic or additive to taking opioid which acts as a sedative.[32]

PASSIVE SIMULATED JOGGING DEVICE EFFORTLESSLY INCREASES PHYSICAL ACTIVITY

Although JD passively moves the lower extremities, it also causes active muscular contraction as evidenced by increased energy expenditure, as measured by increased oxygen consumption.[85] Unpublished studies from our laboratory in 15 women and 11 men, mean age 44 years and mean BMI of 27.9, after conversion of oxygen consumption to METS,[97] revealed that during JD operation, METS increased 15 percent over seated resting posture and 13 percent over supine resting posture. In contrast, METS increased much less, viz., from 4 to 5 percent while standing above sitting at a sit-stand workstation.[98,99] Thus, JD provides a more efficient means to passively increase physical activity than interrupting sitting by standing.

SHEAR STRESS TO VASCULAR ENDOTHELIUM

Endothelial dysfunction is a major factor in the initiation and progression of atherosclerotic lesions of the lower extremities. Prolonged sitting that decreases shear stress to endothelium is specific to the leg vasculature. In its early stages, walking after uninterrupted sitting restores normal leg vascular function. Because the average adult spends most of

the day in the seated posture, lower extremity arteries may be dysfunctional during a major portion of the day and its long-term consequence is peripheral arterial disease.[100,101]

Hemodynamic shear stress, the friction acting upon the vascular endothelium from blood flowing over it, is essential for normal endothelial function. Mechano-sensors located in endothelial cells detect forces of shear stress and convert them into biochemical signals that produce vascular consequences. Among the various shear-induced signaling molecules, NO and reactive oxygen species (ROS) have been implicated in vascular homeostasis and diseases that depend upon three blood flow patterns which comprise (1) laminar or steady, (2) pulsatile, and (3) oscillatory or low flow. Pure flow of each of the preceding occurs only under in vitro conditions whereas combinations take place under in vivo conditions. Physical activity increases both cardiac output and pulse rate to produce a combination of laminar and pulsatile shear stress to the vascular endothelium that stimulates release of beneficial mediators, such as endothelial derived NO into the circulation. Preclinical studies also indicate that moderately increased shear stress upregulates endogenous antioxidant enzymes. Further, shear stress upregulates SIRT1, the anti-ageing molecule, in vascular tissue that includes endothelial cells, monocytes/macrophages, and vascular smooth muscle cells. It is notable that SIRT1 has anti-atherosclerotic and anti-arterial stiffness.[81,102]

Both physical activity and its passive counterpart, JD, increase physiological shear stress to the endothelium. In isolated perfused blood vessels, maximum release of NO into the circulation occurs between 250 and 360 pulses per minute, a speed that can be achieved during natural human fidgeting as well as with usage of JD but not with sustained aerobic exercise.[54] Fidgeting, such as 1 min on and 4 min remaining still for the fidgeting leg while the contralateral leg remained still throughout the fidgeting period as an internal control in 11 young healthy adults at their natural cadence of 220 to 290 taps per minute increased popliteal artery blood flow and shear rate that tapered off after 60 second. Fidgeting did not alter popliteal artery blood flow and shear rate of the contralateral leg, which had reduced blood flow and shear rate throughout the sitting still period. Popliteal artery flow-mediated dilation was impaired after 3 h sitting in the control leg but improved in the fidgeting leg.[103] Therefore, one might think of JD as an effortless, fidgeting device with its major advantage as not being time limited owing to muscle fatigue.

Oscillatory blood flow produces greater amounts of ROS than regular flow patterns (steady or pulsatile) with elevated ROS leading to low NO bioavailability. Low NO bioavailability is partly caused by the reaction of ROS with NO to form peroxynitrite, a molecule that further enhances oxidative stress and upregulation of NADPH oxidase.[104] Both increased physical activity and application of JD mitigate and/or depress NADPH oxidase activity.[105]

In terms of brain microvascular endothelium, physiologic shear causes tightening of cellular junctions but high shear stress and/or high amplitudes of vascular pulsations disrupt them thereby decreasing effectiveness of the blood brain barrier. Reversibility after high shear stress occurs with hemodynamic improvement.

BLOOD PRESSURE RISES DURING PHYSICAL INACTIVITY

In 2017, the American College of Cardiology and American Heart Association (AHA) released new high blood pressure guidelines that lowered the diagnostic threshold of hypertension based upon a large clinical trial called SPRINT. This new treatment threshold lowered a systolic blood pressure greater than 140 mmHg to greater than 130 mm Hg as an effort to reduce prevalence of stroke and myocardial infarction related to hypertension. The new guidelines raised prevalence of hypertension among American adults to 45.6 percent or 103.3 million individuals and were accompanied by the recommendation that 81.9 million take antihypertensive medications. In addition, nonpharmacological interventions were recommended for 9.4 percent of American adults.[106,107]

In the short-term, the onset of a rising blood pressure during uninterrupted sitting or lying as measured continuously with a noninvasive technology in normo- and hypertensive individuals with normal body weight, overweight, or obesity is as brief as 5 to 10 min. In our study of 22 subjects with uninterrupted sitting, peak rise of systolic pressure above the seated control period was 7.5 mmHg and 10.4 mmHg above the supine control period 40 min after a baseline rest period. Corresponding values during JD administration were declines of 8.4 mmHg and 11.2 mmHg of systolic blood pressure in the seated and supine postures, respectively, most likely due

wholly or in part by greater NO bioavailability.[49] JD is an effective technology to acutely lower the elevated blood pressure accompanying physical inactivity, but further studies are necessary to demonstrate effectiveness in long-term and during episodic physical inactivity. In another investigation by others, a rise of blood pressure occurred during uninterrupted sitting in 19 inactive, overweight/obese type 2 diabetics after 7 h as shown by hourly oscillometric measurements.[95]

ENDOTHELIAL DYSFUNCTION

The vascular endothelium has emerged as one of the most important systems affecting health. It responds to humoral, neural, and hemodynamic stimuli and regulates platelet function, inflammation, oxidative stress, and vascular smooth muscle cell growth and migration. It modulates vascular tone by synthesizing and releasing vasoactive substances. Compromised endothelial function is a major contributor to the pathogenesis of cardiovascular disease and correlates with disease progression and prediction of cardiovascular events. Endothelial dysfunction occurs in physical inactivity, accelerated ageing, oxidative stress, inflammation, obesity, excessive alcohol intake, atherosclerosis, type 2 diabetes, smoking, systemic and pulmonary hypertension, metabolic syndrome, chronic obstructive lung disease, sleep apnea syndromes, mental stress, chronic renal disease, stroke, coronary artery disease, autoimmune diseases, rheumatoid arthritis, preeclampsia, cirrhosis, hyperlipidemia, and sepsis among others.

Endothelial dysfunction is ameliorated by increased physical activity that phosphorylates endothelial nitric oxide synthase (eNOS) into an active molecule which reduces oxidative stress and inflammatory cytokines. Normal endothelial function up-regulates superoxide dismutase, down-regulates NADPH oxidase, diminishes uncoupling of eNOS, and reduces ADMA to counteract oxidative stress. Physical activity also increases circulating endothelial progenitor cells, reduces endothelial senescence, improves endothelial repair, increases activation of adenosine monophosphate-activated protein kinase and its activator proteins such as SIRT1 and serine/threonine kinase 11 (LKB1). Most of the preceding changes of biochemical factors have been found in conjunction with WBPA studies. In contrast, polypills that combine multiple vasoactive, cholesterol lowering, and diuretic drugs in a single pill to improve patient compliance are unlikely to directly improve endothelial dysfunction as none increase shear stress, a key factor responsible for normal endothelial function.[108,109]

EFFECTS OF AGEING ON ENDOTHELIAL DYSFUNCTION

Ageing is a major risk for cardiovascular diseases, attributable in part to stiffening of large elastic arteries and endothelial dysfunction. Such risk could be minimized by increased physical activity that increased NO bioavailability and reduced oxidative stress.[110] Endothelial dysfunction occurs in both the macro-and microcirculation with exposure of the vasculature to augmented arterial tone, greater oscillatory shear stress, and elevations of large and small artery stiffnesses. Other lifestyle factors that accelerate endothelial dysfunction include smoking, physical inactivity, excessive alcohol drinking, high salt diet, poor nutrition, and mental stress.[111,112] Through hemodynamic alterations and living an unhealthy lifestyle, endothelial dysfunction becomes an important contributor to age-dependent, increased prevalence of hypertension and atherosclerosis.[113]

MANAGEMENT OF ENDOTHELIAL DYSFUNCTION

Moderate intensity physical activity as recommended by AHA and leading a healthy lifestyle improves endothelial dysfunction by increasing NO bioavailability.[114] However, only about 20 percent of American adults adhere to AHA exercise recommendations.[115] In addition to inadequate exercise, prolonged uninterrupted sitting also leads to endothelial dysfunction.[101] It has not yet been demonstrated that substituting sitting with light intensity physical activity, such as standing and low pace walking, raises shear stress to a level that returns significant endothelial dysfunction to normal.[113,116] Self-administration of JD allows one to remain sitting while still benefitting from increased shear stress to increase NO bioavailability.[49,84] In part, habitual aerobic exercise also prevents the age-related decline in endothelial function due to nuclear factor kappa beta (NF-κB) signaling of inflammatory factors. Inhibition of NF-κB signaling has therapeutic potential in individuals who are unable or unwilling to perform regular aerobic exercise.[117] In a sheep asthma model, WBPA administered with the motion platform to increase NO

bioavailability blocked NF-κB activity during the late, inflammatory phase of the asthma reaction.[56] Therefore, JD might also benefit in the same way as the motion platform helps individuals who are unable or unwilling to increase physical activity.[117]

OLDER ADULTS NEEDING OPIOID REPLACEMENT THERAPY

The reason for discussing "arterial stiffness" during accelerated ageing with opioid addiction is that oxidative stress has a common basis to both situations which might be additive and synergistic in their action.[118-121] Further, the current ageing population that began experimenting with substance abuse decades ago belongs to a group that will increase their need for substance abuse treatments as they age. In the United States, the number of adults 50 years of age or older requiring treatment for problematic substance use will increase from 1.7 million in 2000 to 4.4 million in 2020.[122] This increased need for treatment is quite apparent among older adults in methadone maintenance treatment (MMT) clinics. The effectiveness of MMT in decreasing risk of premature death and the rapidly growing rate of older adults in North America, has resulted in some patients being prescribed methadone for decades. These high rates relate to the large-scale enrollment of MMT in North America in the 1970s, where many who entered in their twenties are now in midlife and older. This group is generally aging more quickly than the general population because of past and present lifestyle choices that has led to its consequences.[118] Treatment with the JD might slow progress of accelerated vascular ageing in the presence of OUD but long-term studies are needed for corroboration.

AORTIC STIFFNESS AND SMALL VESSEL DISEASE

Arterial stiffness, particularly of the aorta, begins in young adulthood due to anatomical alterations of vascular walls produced by the backward pulse wave reflected from the periphery which augments central systolic blood pressure. Stiffness progressively accelerates in the fifth decade and continues until death.[123] The augmented systolic pressure wave is transmitted to midsize and smaller arteries resulting in structural damage and dysfunction of cerebral, coronary, and renal arteries.[102] The latter, called small vessel disease, can be demonstrated in the brain with neuroimaging techniques. The greater age-related, aortic stiffness and high-pressure pulsations excessively increase ventricular work such that left ventricular mass is increased.

Small vessel disease constitutes the basis for the most prevalent ischemic brain disorder, vascular cognitive dysfunction. As a risk in ageing, it is the commonest vascular cause of dementia as well as being responsible for about one fifth of all strokes worldwide. Manifestations of cerebral small vessel disease include early cognitive impairment with limited capacity to utilize complex information, to formulate strategies, and to exercise self-control. Episodic memory deficits occur but are less severe than those in patients with Alzheimer's disease. Neuroimaging abnormalities include silent lacunar infarcts, white matter hyperintensities, and microbleeds. Accompanying depressive symptoms correlate with greater degrees of arterial stiffness.[124,125] Since opioid use disorder accelerates vascular ageing,[119] this factor puts opioid addicts at additional risk for cerebral, coronary, and renal complications but no systematic evaluation of this issue has yet been reported.

CORONARY MICROVASCULAR DYSFUNCTION

Aortic stiffening associated with ageing predisposes to angina without coronary artery obstruction because repeated exposures to the large reflected pulse pressure wave originating in the ageing aorta damages the walls of coronary arteries. It occurs predominately in women, has substantial morbidity, is present in 10 percent to 30 percent of patients undergoing angiography, and persists after revascularized coronary artery procedures. Its diagnosis is based in part on measurements of CFR, the maximal increase in coronary blood flow above its resting level for a given perfusion pressure when the coronary vasculature is maximally dilated as with infusion of adenosine. Coronary microvascular dysfunction is present in 50 percent to 65 percent of patients with values of CFR or myocardial perfusion reserve <2.5 in the absence of coronary artery stenosis measured with Doppler echocardiography, positron emission tomography, cardiac magnetic resonance imaging, dilution methods, or intracoronary Doppler.[126-128] Opioid addiction might be a risk factor for coronary microvascular owing to wave reflection from the ageing aorta, but this risk has not been rigorously investigated.[129] There have not been any short-term, effective, pharmacotherapies or surgical procedures available for coronary microvascular dysfunction. Adherence to

a healthy lifestyle has been a long-term fall back recommendation.[130]

Using the motion platform, Fukuda et al.[74] administered a single session of WBPA to 15 healthy subjects and 20 patients with coronary artery disease. Flow velocity in the distal portion of the left anterior descending coronary artery was measured with transthoracic Doppler echocardiography at baseline and during adenosine infusion. CFR was calculated as the ratio of hyperemic to basal mean diastolic flow velocity. WBPA increased CFR a mean from 3.3 to 3.7 in 35 patients. Coronary angiography showed significant LAD narrowing in eight of the 20 patients with coronary artery disease but WBPA increased CFR from 2.4 to 2.7 in them as well.

In anesthetized swine, our laboratory reported that a single WBPA session in conjunction with injection of colored microspheres increased epicardial blood flow 71 percent and endocardial blood flow 93 percent.[59] Since treatment with WPBA and our passive simulated JD have the same basis in increasing pulsatile shear stress to the endothelium, we assume that JD would have the same outcome for treating and preventing coronary microvascular dysfunction.

PREVENTION AND TREATMENT OF VASCULAR STIFFNESS

Currently, there are not any rigorous demonstrated means for acute, effective, treatment of arterial stiffness. Moderate-to-vigorous physical activity and reduction of sedentary behavior are each associated with slower age-related progression of aortic stiffness independent of conventional vascular risk factors that take place over months, longer, or never in the elderly with concurrent hypertension.[131-133] Early vascular aging is an asymptomatic condition and can only be currently diagnosed with measurements of pulse wave velocity that show a rapid transit time of the pulse wave from one vessel to another or to the heart.[121] Rodent studies indicate that low bioavailability of NO predisposes to aortic stiffness[134] and therefore, chronic usage of JD might reduce severity of aortic stiffness but benefit of this intervention has not yet been established.

With ageing, the walls of large arteries, particularly the aorta, become thicker and less elastic thereby increasing pulse wave velocity such that systolic and pulse pressure increase. Arterial stiffening is a predictor of several cardiovascular outcomes, such as stroke, myocardial infarction, and chronic kidney disease. Increased aortic stiffness is associated with the higher risk of incident hypertension. As central arteries become stiffer, they maintain their conduit function, but progressively lose their buffering properties and transmit high energy pulse pressure into the vascular bed of organs highly vascularized but prepared only to deal with a near continuous flow of blood, like the blood vessels of the brain and kidneys. Stiffer arteries transmit not only the forward, but also the reflected, backward pressure waves with higher velocity, and eventually with greater amplitude.[131] Although noninvasive, pulse wave velocity measurement technology has been available for some time, it has not yet reached the mainstream of clinical diagnostics. This might relate to the lack of symptoms of stiffened arteries until long-term effects create clinical complications in target organs.

OXIDATIVE STRESS WITH AGEING

Ageing of organs by accumulation of ROS promotes oxidative collateral damage. Increased oxidative stress produced in the mitochondria and cytosol of heart and brain is a common denominator to almost all cardiovascular and cerebrovascular diseases. One of the most accepted theories regarding the mechanism of aging is that ROS produced during normal aerobic metabolism tend to accumulate with age ultimately resulting in oxidative damage of genomic DNA, proteins, and cellular components. An increase in pro-oxidants promotes whereas improvement of antioxidant defenses delays the ageing process.[81,135]

Cellular ageing is a function of telomere length that shortens with each cell division, up to a critical length that results in replicative senescence. This is a permanent, nondividing state which ensues in somatic cells after a predetermined number of cell divisions. Telomerase is an enzyme responsible for maintaining the length of telomeres and is upregulated by increased bioavailability of NO to minimize cellular senescence.[136] An endogenous produced molecule, SIRT1 that is increased by shear stress to the endothelium also delays vascular aging through its antioxidant properties. It increases activity of catalase and manganese superoxide dismutase, two key enzymes involved in controlling cellular ROS levels. SIRT1 expression and activity gradually decrease with ageing while oxidative stress, the major contributing cause of atherosclerosis, increases.[81,135]

CEREBRAL BLOOD FLOW DURING PHYSICAL ACTIVITY AND WBPA

There has been a paucity of publications dealing with regional microvascular blood flows during physical activity as measured with labeled microspheres. Two investigations in swine trained to run on a treadmill for 20-30 min at 75-80 percent of their maximum heart rate revealed that cerebral microvascular blood flow did not change from rest in contrast to 130 percent increase of myocardial and 210 percent increase of skeletal muscle microvascular blood flows. Renal cortex, gastric mucosa, ileal mucosa, and spleen microvascular blood flows decreased 10-60 percent from resting values while liver blood flow remained unchanged.[137,138] In an investigation of anesthetized swine from our laboratory, measurement of regional microvascular blood flows using color labeled microspheres were obtained 10 min after application of WBPA and 10 min after its cessation. During WBPA, cerebral and brain stem blood flows increased 180 percent above control values whereas endocardial, epicardial, renal cortex, ileal mucosa, gastric mucosa, and liver blood flows increased 50-90 percent above control values. Skeletal muscle and spleen blood flows during WBPA remained unchanged. Elevated organ microvascular blood flows with WBPA returned to control values after stopping WBPA with exception of epicardial and endocardial blood flows that remained elevated another 10 min when the study was terminated.[59] The differences between active exercise and passive body movements appear to depend upon tissue demands, eg, WBPA increased shear stress to the endothelium by vasodilation without tissue demand in contrast to demand for oxygenated blood by contracting cardiac and skeletal muscle during exercise. If such results in swine can be confirmed in humans, long-term application of JD might be an effective strategy to increase cerebral microvascular blood flow in order to minimize the cognitive dysfunction present in vascular dementia due to ageing and/or abuse of opioids.[139-141]

ACCELERATED VASCULAR AGEING WITH OPIOIDS

Individuals taking opioids for chronic pain over 5 years have a greater degree of arterial stiffness than nonopioid controls, and this difference is more marked in women than men.[120] The degree of arterial stiffness relates to the vascular age, central systolic pressure, and subendocardial perfusion ratio by the specific opioid drug taken. Of three FDA-approved drugs for opioid addiction, eg, buprenorphine, methadone, and naltrexone, methadone was uniformly associated with poorer arterial and vascular outcomes, both alone and interaction with chronologic age and other established risk factors. These data were equivalent to advancement in vascular age at a modeled chronologic age of 60 years to 72.3 (buprenorphine), 82.8 (methadone), and 72.4 years (naltrexone) compared to nonopioid user controls (67.4 years).[119]

Increased oxidative stress accelerates vascular ageing through endothelial dysfunction marked in part by progressive decrease of NO bioavailability caused by eNOS uncoupling. The latter converts L-arginine to the oxidizing molecule superoxide, owing to increased NADPH oxidase activity. Superoxide reacts with NO to form peroxynitrite which promotes additional eNOS uncoupling and acceleration of the atherosclerotic process.[142] Heroin abuse and natural ageing both affect immunological cell functioning, eg, heroin use is associated with premature aging at both cellular and brain system levels. Indicators of ageing included peripheral blood telomerase activity, which reflects cellular aging, and both structural and functional measures of brain magnetic resonance imaging. Heroin users have significantly low telomerase activity which interacts with heroin use to disturb structural integrity of gray and white matter of the prefrontal cortex in a key brain region implicated in ageing. Reduced telomerase activity interacts with heroin use to impact age-sensitive brain functional networks which correlates with behavioral performance on executive functioning, memory, and attentional control.[143] Since JD upregulates antioxidant defenses,[65] its application should be a component of any plan for opioid withdrawal.

In terms of oxidative stress, accelerated vascular ageing and OUD may be synergistic or additive. Oxidative stress caused by opioids derives from direct or indirect effects of the phases of opioid exposure and its withdrawal. Increase in the levels of oxidants compared to antioxidant defense systems leads to cellular dysfunction and eventually to cellular death. A great deal of such evidence derives from preclinical research of morphine and heroin in laboratory rodents.[144] Here, high-dose morphine produces

endothelial dysfunction by decreasing endothelium-derived NO bioavailability and generating superoxide by activation of NAPDH oxidase.[145] Increasing vascular shear stress by the motion platform and JD improve endothelial dysfunction.[76,146]

OPIOID TOLERANCE, OXIDATIVE STRESS, AND ANTIOXIDANT PROPERTIES

Tolerance to opioids necessitates escalating their dosage to achieve equivalent pain relief, even as the onset of opioid-induced hypersensitivity subverts the therapeutic impact of such increases. Tolerance decreases QoL in patients with chronic pain due to over-sedation, physical inactivity, respiratory depression, constipation, and risk of addiction. Further, nitroxidative stress is a major contributor to pathogenesis of pain and plays an important role in opioid antinociceptive tolerance, caused by the superoxide, O_{2}-, nitric oxide, NO, and peroxynitrite $ONOO^-$ or its protonated counterpart ONOOH, the product of their interactions.[147] Both WBPA and JD can restore endothelial function by increasing eNOS expression, decreasing eNOS uncoupling, reducing ($ONOO^-$) levels (nitroxidative stress), and shifting [NO]/[$ONOO^-$] balance toward NO.[148]

The antioxidant properties of WBPA have been evaluated in normal mice and mice with high levels of oxidative stress, eg, type 1 diabetes and Duchene Muscular Dystrophy. Whole-body periodic acceleration upregulates eNOS and increases expression of endogenous antioxidants that include glutathioneperoxidase-1 (GPX-1), catalase (CAT), and superoxide dismutase 1 (SOD1).

These compounds increase total antioxidant capacity along with the antioxidant response element transcription factor Nrf2 translocation to the nucleus. Such actions decrease ROS in both mice models of oxidative stress. Therefore, WBPA as well as its JD counterpart can serve as nonpharmacologic means to counteract the increased oxidative stress produced by administration of opioids.[65]

Depending upon a specific opioid, chronic analgesia and reward may diverge in their effects. An increase of opioid amount may be needed to counteract the diminution of the euphoric effect over time without increasing analgesic effectiveness and vice versa. In preclinical studies, opioids activate inflammatory cytokines, most notably tumor necrosis factor-α.[149,150] Reduction of inflammatory cytokines can be accomplished by WBPA or JD potentially decreasing tolerance to opioids, but this preclinical effect requires confirmation in OUD patients.[56,65,66,88,149]

NEUROTROPHIC FACTORS AND OPIOIDS

Opioid administration to rodents produces rapid onset of addictive behaviors that simulate human addiction. Complicated relations among neurotrophic factors and NO in opioid addicted rodents are not well understood. Investigations of the pathophysiology have focused on reduced levels at regional, cerebral locations of neurotrophic factors, and cerebral blood flow. BDNF and GDNF are the major neurotrophic factors critical for the growth, survival, and differentiation of developing neurons. These factors also are important for the survival and function of adult neurons, learning and memory, and synaptic plasticity.

Studies have been conducted of the role of BDNF and GDNF upon the behavioral effects of opioids and in the neuroadaptations induced by their repeated exposure in the mesocorticolimbic dopamine system of rodents. Whether BDNF and/or GDNF facilitate or inhibit drug-taking behaviors are dependent upon the drug type, brain site, the addiction phase (initiation, maintenance, or abstinence/relapse), and the time interval between site specific administration of BDNF or GDNF into the brain and the analysis of reward- and relapse-related behavioral assessments.[35,151] The role of BDNF and GDNF is hampered by the fact that such molecules injected into the circulation are ineffective because they are too large to cross the blood-brain barrier and hence their infusion directly into the brain is not a viable human option.

Brain-derived neurotrophic factor is a key positive regulator of neural plasticity that promotes the actions of stimulant drugs of abuse such as cocaine. However, BDNF appears to play an opposite role for in responses to morphine and presumably other opioids, administered to mice by subcutaneous pellets or intermittent intraperitoneal injections. Suppression of BDNF in the ventral tegmental area (VTA) of mice enhances ability of morphine to increase dopamine (DA) neuron excitability and promote reward. During withdrawal of morphine in addicted mice, there is a marked upregulation of BDNF and interaction between brain NO and BDNF levels.[35,152] GDNF's role in opioid addiction is less understood than BDNF.[153]

In daily 1-h WBPA treatments for 2 weeks in 20 normal mice compared to a nontreated, control group, whole brain homogenates were analyzed for eNOS, p-eNOS (phosphorylated eNOS), BDNF, and GDNF. WBPA significantly increased brain protein levels of BDNF, GDNF, and the ratio of active (p-eNOS) to total eNOS 30 percent above control values in whole brain homogenates. These values were within the range reported by other investigators for the effects of exercise.[61] This study did not investigate the BDNF source within the brain but recently others have found that BDNF is secreted by cerebral endothelium.[154,155]

In another study from our laboratory, it was shown that insufficient dystrophin in cortical neurons of a mouse model of muscular dystrophy (MD mice) was associated with elevated resting intracellular Ca2+ and Na+, increased oxidative stress, neuronal damage, and cognitive deficit.[64] In a follow-up study, WBPA applied 1 h daily for eight consecutive days to MD mice increased BDNF levels of cerebral cortex homogenates 1.8-fold, GDNF 1.6-fold, and eNOS 1.8-fold. Improvement of cognitive performance also took place.[156]

BRAIN–DERIVED NEUROTROPHIC FACTOR SECRETED BY CEREBRAL ENDOTHELIUM

Brain-derived neurotrophic factor levels present in brain homogenates correspond mainly to BDNF present in cerebral endothelial cells which is dependent on cerebrovascular endothelial eNOS activity. Low-cerebral levels of BDNF have been implicated in neurodegenerative, neurological, and psychiatric diseases. Increasing BDNF levels in the brain have potential to prevent and treat chronic brain diseases. Since BDNF expressed by the cerebral endothelium largely accounts for BDNF levels present in the brain, it is likely that BDNF-based therapies would be most effective if they also targeted cerebral eNOS. Most of the BDNF found in the brain corresponds to BDNF present in the cerebral endothelium and endothelium-derived NO is a regulator of cerebrovascular BDNF production. It has been estimated that the human brain contains equal numbers of neurons and non-neuronal cells and that endothelial cells represent 17 percent of the cell population at least in the rat cortex, with neurons accounting for 47 percent. Given the density of endothelial cells and their ability to synthesize and secrete large quantities of mature BDNF (mBDNF), endothelial mBDNF should be considered as a link connecting brain with endothelial health. The discovery that mBDNF is secreted by cerebral endothelial cells suggests that improvement of brain health should target cerebral endothelial cells rather than neurons.

Long-lasting changes in synaptic efficacy mediate long-term memory through two secretory proteins, tPA and BDNF. tPA, by activating plasmin, converts the precursor proBDNF to its mature BDNF (mBDNF) that is critical for memory expression.[157] Both components of this process are produced by increased pulsatile shear stress to the endothelium as administered with WBPA or JD.

RECENT PHARMACOLOGICAL TREATMENT FOR OPIOID USE DISORDER

Up until 2018, only three drugs, methadone, buprenorphine, and naltrexone, were approved by FDA for treating opioid addiction. These drugs have been usually prescribed as a component of MAT, a program of behavioral treatments in structured settings, or to prevent relapse after detoxification and stabilization. Behavioral interventions were utilized to improve medication compliance and target problems not addressed with medication alone such as comorbid psychiatric and substance use conditions, that were not exclusionary for initiating MAT but required attentive evaluation and monitoring owing to potential of reduction of effectiveness.[157] About 23 percent of people exposed to opioids develop OUD, a risk for transition to addiction second only to tobacco (32 percent) and higher than that for cocaine (17 percent), alcohol (15 percent), or cannabis (9 percent).[159] Further, six percent of individuals prescribed opioids continue to use them at greater than one year, a risk for habitual lifetime use that increases exponentially after five days of initial exposure. Since nonmedical opioid use is a gateway to potential heroin addiction, an early intervention must be considered as a medical emergency.[160]

In May 2018, FDA approved the fourth drug for management of OUD, lofexidine, to be taken daily up to 14 days for ameliorating symptoms of opioid withdrawal. Lofexidine is an α2-adrenoceptor agonist that decreases norepinephrine outflow from the central nervous system responsible for symptoms of sudden opioid withdrawal. Lofexidine is a structural analog of clonidine, also an α2-adrenoceptor agonist that is approved for hypertension therapy but

used off-label since 1980 to ameliorate symptoms of opioid withdrawal. In managing opioid addiction, withdrawal mitigation strategies are key to ultimate cessation of opioid usage. Withdrawal symptoms such as extreme anxiety, fear, aversion, and pain can be terrifying to opioid-dependent individuals. Even in those individuals who urgently want to stop taking opioids, the fear of such symptoms is among the main reasons they continued to abuse opioids.[44]

STAGES OF OPIOID DEPENDENCE

There are four stages of opioid dependence that require surveillance, eg, (1) initiation, (2) stabilization and maintenance, (3) withdrawal (detoxification) and (4) relapse prevention.

Initiation of opioid dependence: Here, the goal is to withhold opioids completely while providing nonopioid therapies. This stage often occurs from overprescribing opioids stemming for relief of both acute and chronic pain.

Stabilization or maintenance is accomplished by opioid substitution treatments using FDA-approved drugs, methadone, or buprenorphine in a way to ensure that the drug use becomes independent of mental state such as craving and mood as well as finance and physical location. Access to easy enrollment and maintenance in such programs helps prevent reliance on street heroin and promotes retention but reports of long-term outcomes are lacking.[161] Clearly, there is need for alternate means to improve stabilization. In this respect, the concurrent administration of JD for 30 min 2 to 3 times a day might be helpful because NO release from cerebral endothelium down-regulates the action of norepinephrine, a molecule responsible for the adverse symptoms of opioid withdrawal.[162]

Withdrawal: Recently, FDA-approved lofexidine administration for up to 14 days usage for treatment of opioid withdrawal.[171] This drug belongs to the class of α2-adrenoceptor agonists that are approved for treatment of hypertension. Drugs in this class suppress symptoms related to outflowing of norepinephrine from the central nervous system associated with opioid withdrawal. Since 1980, clonidine, a drug used for hypertension and of the same class as lofexidine has been an off-label therapy for symptomatic relief of the opioid withdrawal syndrome.[44,163-165]

Prevention of relapses: Injected naltrexone, an opioid antagonist, offers prevention after inpatient detoxification but with mixed long-term success.[166]

To summarize, current technologies have not made a major impact on treatment of OUD or its combination with chronic pain. With exception of the initiation stage which relates mainly to overprescribing opioids and providing inappropriate, long-term prescriptions, Gentle Jogger JD as described in this review has potential to be the first safe, noninvasive device to be useful through the initiation, stabilization and maintenance, withdrawal and relapse prevention phases of opioid dependence. It should be recalled that opioids promote accelerated vascular ageing, oxidative stress, inflammation, and impaired QoL including physical inactivity and therefore can be considered cofactors affecting opioid dependence.[120,144,167] The JD technology mitigates the preceding by providing effortless physical activity even during uninterrupted prolonged sitting while reducing oxidative stress and inflammation by increasing bioavailability of NO and upregulating antioxidant defenses.[49,56,65,168-170]

α2 ADRENOCEPTOR AGONISTS IN OPIOID USE WITHDRAWAL

α2 adrenoceptor agonists play an important but limited role in management of OUD. This is because they have not been approved by FDA for all stages of stabilization, tapering, and relapse prevention.

Chronic intake of high-dose opioids produces tolerance to its effects leading to taking higher doses to achieve sufficient analgesia thereby risking oversedation and respiratory depression. Chronic opioid exposure modulates neurons in the brain stem that stimulate wakefulness, respiration, blood pressure, and general alertness. Many such neurons are noradrenergic in function along with high density of presynaptic μ-opioid receptors. When these μ-opioid receptors are stimulated by large amounts of opioid agonists as occurs in tolerance and overdose, such neurons suppress their normal release of norepinephrine thereby causing drowsiness, decreased respiratory drive, and lowered blood pressure. Sudden removal of the opioid-induced inhibition of these cells causes excessive release of norepinephrine that elicits jitters, anxiety, increased respiratory rate and blood pressure, muscle cramps, and diarrhea. This phenomenon has been confirmed by the finding of elevated plasma levels of MHPG (3-Methoxy-4-hydroxyphenylglycol), the major metabolite of norepinephrine.[172] Other symptoms of sudden withdrawal include hypersensitivity to pain, irritability,

insomnia, skin piloerection, and an influenza-like syndrome characterized by rhinorrhea, lacrimation, and myalgias due to opioid removal from other brain regions.

α2 adrenoceptor agonists require the presence of brain eNOS for their central activity. In eNOS knockout mice, in which eNOS is absent, the central hypotensive effect of injected dexmedetomidine (an α2 adrenoceptor agonist) is abolished. In the presence of eNOS, this drug that has analgesic and sedative properties also decreases need for medically related opioid consumption.[173-175] Thus, eNOS is required for the central hypotensive effect, the sedative and analgesic effects of α2 adrenoceptor agonists. Norepinephrine outflow from the brain is upregulated in opioid withdrawal as well as during inadequate opioid dosing in stabilization and tapering of opioid dosing thereby giving rise to vasoconstriction and withdrawal symptoms. Both the passive-simulated JD and exercise-stimulated cerebral eNOS by increasing endothelial shear stress promote the release of NO from cerebral endothelium. These activities produce central vasodilation that counteracts vasoconstriction caused by norepinephrine. This highlights the potential for JD acting alone or together with α2 adrenoceptor agonists to facilitate opioid stabilization, tapering and withdrawal, and relapse prevention.[61,161,176-178]

PAIN AND OPIOID DEPENDENCE

In recent years, the prevalence of chronic pain has been worsening rather than improving. Both patients and medical practitioners often labor under the mistaken idea that most pain problems can be fixed with a drug or procedure. Patients are often regarded as passive participants with little emphasis placed on therapies that engage pain preventive and self-care strategies. The current opioid crisis, fueled in large part by physicians overprescribing opioids for pain relief, has brought about the issue of managing chronic pain in the presence of opioid dependence. Such patients often continue to experience severe pain despite long-term administration of high-dose, opioid therapy. Further, high prevalence of prior SUDs, psychiatric and medical comorbidities compound this issue. There is urgent need of plans to treat disabling, chronic pain in individuals with co-existing opioid dependence, and medical co-morbidities.[40,170] About 12.5 percent of the 92 million US adults who took prescription opioids in 2015 misused them. Although those without prescription opioid use disorder reported pain as the most common reason for misuse (63 percent), more than half of the rest cited other reasons, such as "relaxing" and "getting high." As the opportunity to access prescription opioids is waning among individuals with OUD, concurrent taking of street heroin is steadily increasing. Although it is often assumed that chronic pain precedes onset of SUDs, it appears that SUDs typically precedes onset of chronic pain among those individuals with both conditions.[20,179]

TRANSITION FROM EARLY TO ESTABLISHED CHRONIC PAIN

Psychosocial pain factors. Early development of chronic pain is associated with (1) stress, (2) physical inactivity, (3) belief in persistent injury, (4) falls and fear of falling, (5) fear of physical activity, and (5) over-reliance on pain medications.

Comorbidities. Chronic pain becomes established in the presence of (1) psychiatric disorders, (2) medical illness with significant psychological impact, (3) dependence, SUD, and (3) various prescribed medications.

Disabling chronic pain, particularly among those with SUD, often presents as multimorbidity involving varying combinations of several chronic pain conditions, psychiatric and medical comorbidities, polysubstance, and medication dependencies. Such patients are at risk to suicide, overdose, and all-cause mortality. Isolated focus on a single issue or limited set of issues like pain and SUD without coordinated treatment of multiple comorbidities is unlikely to lead to sustained benefit. Disabling chronic pain requires specialized healthcare, a full discussion which is beyond the scope of this paper. In a related comment, Manhapra and Becker[41] stated "It is essential to recognize that traditional biomedically oriented treatment with a focus on pharmacotherapy and passive interventions should be abandoned as the primary treatment of chronic pain, especially[50] among those with comorbid SUD/medication dependence. "Reexplaining pain," a psychological teaching tool, followed by the effective management of SUD/medication dependence, comorbidities, and polypharmacy, combined with simple behavioral activation (eg, walking 30 minutes twice a day at a comfortable speed), are effective for many patients." According to Sackner et al.[49], using JD to increase pulsatile shear stress to the endothelium has greater effectiveness for pain relief than leisurely walking. Chronic pain, one of the commonest reasons that adults seek medical care, has

been linked to restrictions in mobility and daily activities, dependence on opioids, anxiety and depression, and poor perceived health or reduced QoL. Chronic pain among US adults ranges from 1 percent to 40 percent. High-impact chronic pain is characterized by its limitation of life or work activities.

Neuropathic and inflammatory pain

Noxious stimuli are detected by sensory nerve fibers called nociceptors that are free nerve endings which terminate in the superficial layers of the dorsal horn of the spinal cord.

Clinical pain arises either from damage to the nervous system (neuropathic pain) or neuroinflammation (inflammatory pain). Neuropathic pain, a clinical diagnosis, refers to pain caused by pathology of the central or peripheral nervous system. Such pain is typically described as shock-like or burning in nature, often with hyperalgesia (an increase in the response to noxious stimuli), and allodynia (the presence of pain in response to normally innocuous stimuli). A wide variety of painful conditions have a component of neuropathic pain, that include traumatic injury, nerve compression, radiculopathies, cancer metastases, diabetic neuropathy, postherpetic neuralgia, and HIV-associated neuropathy among others. Inflammatory pain has classically been understood as pain secondary to inflammation from tissue damage. Treatment approaches may differ depending on the type of pain identified. However, the two pain types may merge since inflammation at an affected nerve may play a role in mediating neuropathic pain. Peripheral nerve damage activates glial cells, which release inflammatory mediators and stimulate production of pain signaling molecules such as glutamate, substance P, and calcitonin gene-related peptide. Prolonged release of proinflammatory mediators causes central nervous system changes that may result in neuropathic pain. Thus, distinctions between the two pain types becomes blurred as various shared mechanisms are identified.

Inflammation produces release of a variety of agents (bradykinin, cytokines, eicosanoids, serotonin, histamine, cations), that lead to nociception. The pharmacological control of inflammatory pain is based upon two strategies. The first involves drugs that inhibit nociceptor sensitization, and therefore, hypernociception which is the main action of aspirin that, by inhibiting cyclooxygenases, prevent nociceptor sensitization. The second strategy involves directly blocking ongoing pain, resulting in antinociception as achieved by opioids and NO. Although NO mediates nociception and is unequivocally involved in central sensitization; experimental and clinical investigations indicate that NO is also capable of analgesia. The antinociceptive effect of NO is consistent, and its clinical application is an important pain therapy strategy. Further, modification of preexisting analgesic and anti-inflammatory drugs by the addition of NO-releasing moieties improves the analgesic efficacy of these drugs as well as reducing their side effects. Nitric oxide plays a complex and diverse role in the modulation of nociceptive transmission in both the peripheral and central nervous system. The mechanisms involved in the nociceptive as well antinociceptive effects of NO have not yet been fully characterized, and their discussion is beyond the scope of this paper. Nevertheless, there is strong evidence that NO induces analgesia and also mediates the peripheral and central antinociceptive effect of analgesic compounds, such as opioids and anti-inflammatory drugs.[168] Immune system activation has been shown to facilitate and increase neuropathic pain. Several pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-17, are increased in animal models of neuropathic pain as well as in the cerebrospinal fluid and blood of patients with chronic neuropathic pain conditions. Therefore, pharmacologically lowering the levels of inflammatory cytokines may reduce pain, which has been demonstrated for various cytokines in both animal and clinical studies.[180]

CHRONIC PAIN PREVALENCE

As many as 20 percent to 50 percent of postpubertal adolescents suffer from persistent pain. In young adults, prevalence estimates for any pain in the previous 6 months are 77 percent, whereas chronic and disabling pain estimates range from 4 percent to 14 percent. Disabling pain in young adults remains poorly characterized but QoL is reduced and associated with number of pain sites and intensity. With respect to additional key health behaviors that may impact pain interference in young adults, these include cigarette smoking, alcohol use, poor sleep quality and quantity, and obesity. Back pain is the most commonly location for pain, comprising 60 percent of primary pain location, with most of unknown etiology.[181] Estimates of prevalence vary widely such that chronic pain may be

present in approximately 100 million US adults. Twenty million US adults have high-impact chronic pain, with higher prevalence among women, older adults, previously but not currently employed adults, adults living in poverty, adults with public health insurance, and rural residents as well as those with lower levels of education and among adults with private health insurance.[39]

Increased oxidative stress and inflammation in chronic pain

Chronic pain, refractory to over-the-counter analgesic drugs is a major health issue. While selective cyclooxygenase-2 (COX-2) inhibitors are effective in certain types of chronic pain, their usefulness is limited owing to their increased risks of myocardial infarction and stroke. The clinical utility of opioids is hampered by rapid onset of dependence and analgesic tolerance. The latter necessitates escalating the amount and frequency of opioid dosing to achieve desired analgesia. Prolonged administration of opioids produces debilitating side effects of over-sedation, physical inactivity, respiratory depression, constipation, and addiction.[147] Despite their sedative action association with physical inactivity, little attention has been paid to this harmful side-effect of opioid dependence.

Both opioid dependence and physical inactivity promote oxidative stress, inflammation, and endothelial dysfunction.[167,182-184] Such factors contribute to pathogenesis of noncommunicable diseases and premature mortality. Whether they are additive or synergistic in action has not yet been determined but considerable evidence implicates oxidative stress of superoxide (SO) and peroxynitrite (PN) as contributing to chronic pain and transition from acute to chronic pain. Increased pulsatile shear stress as occurs with JD inhibits SO and PN formation with potential to prevent and reverse the characteristic pathologies associated with inflammatory pain, neuropathic pain, and opioid-induced hyperalgesia and tolerance.[185]

Opioids in presence of chronic pain

In 2014, US retail pharmacies dispensed 245 million prescriptions for opioid pain relievers. About 65 percent were for short-term therapy (<3 weeks), but longer-term opioid therapy was prescribed for 3-4 percent of the adult population (9.6 million to 11.5 million persons). Benefits of opioids prescribed for chronic pain are much more questionable. Repeated administration of any opioid almost inevitably causes tolerance and physical dependence. Short-term results of repeated opioid administration resolve rapidly after discontinuation of opioids, ie, in a few days to a few weeks, depending on the duration of exposure, type of opioid, and dose. The rewarding effects of opioids play a major role in the risks of opioid diversion, overdose, and addiction. These risks are present with all opioids and with all pain diagnoses. No single or simple change in prescribing behavior can be expected to alleviate all risks while managing pain. Strategies that can help mitigate risks include limiting the prescribed opioid to the lowest effective dose for the shortest effective duration for both acute and chronic pain. Regular monitoring and reassessment minimize risks of long-term opioid use by tapering and discontinuing opioids among patients who are not receiving clear benefits or among those who are engaging in practices that increase the risk of overdose such as substance abuse. Estimates of iatrogenic addiction vary considerably from less than 1 percent to more than 26 percent. About 4 percent of individuals who are addicted to prescription opioids transition to heroin, possibly because heroin is typically cheaper and often easier to obtain than dispensing of prescription opioids which are highly regulated by governmental agencies. Unlike tolerance and dependence, addiction is not predictable as a result of opioid prescribing.[186]

In an FDA statement released in April 2019, the agency stated it is adding a warning about sudden discontinuation of use to the prescribing information of opioid painkillers such as OxyContin (oxycodone), Vicodin (hydrocodone), morphine, and other drugs. “Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms,” the agency explained. “In turn, these symptoms can lead patients to seek other sources of opioid pain medicines, which may be confused with drug-seeking for abuse. Patients may attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.” The new guideline is meant to help doctors allow patients who no longer require an opioid to safely wean themselves off the drug—cutting their risk for withdrawal symptoms. It might be worthwhile to initiate administration of JD during this process.

Patients with OUD maintained on methadone have greater chronic pain than the general population. In a methadone-maintenance clinic comprising 227 patients, 60 percent reported chronic pain and needed

a higher mean methadone dose, than those without chronic pain. Pain was primarily located in the lower extremities (59 percent) and back (51 percent).

Only 13 percent of patients with pain received pain management, and few were being treated with any nonopioid adjuvant analgesics. Yet patients who received treatment reported 51 percent improvement of pain. This indicates that more efforts should be directed to provide standard pain management techniques to patients with OUD to reduce their overall level of pain and potentially improve their treatment outcomes.[187] For chronic pain management in opioid-dependent patients, their discontinuation requires dose tapering to prevent symptoms of withdrawal. In some patients, repeated use of opioids produce hyperalgesia, a state of heightened pain sensitivity. Hyperalgesia can lead to inappropriate increases in opioid dosing which exacerbates rather than ameliorates pain. If hyperalgesia occurs, dose tapering or tapering to discontinuation is the preferred approach to pain relief.[18]

CHRONIC AND SUBACUTE PAIN CONDITIONS

Chronic and subacute pain conditions have pathogenic, genetic, or biologic origins for their basis or an idiopathic source for the symptoms. Chronic pain defined, as persistence greater than 90 days, includes various forms of arthritis, connective tissue diseases, postherpetic neuralgia, peripheral neuropathy, Duchenne muscular dystrophy, and sickle cell anemia, as diagnosed through biologic or inflammatory markers, radiologic evidence, or tissue damage. Idiopathic conditions, that often rely entirely on subjective complaints, include complex regional pain syndrome, fibromyalgia, chronic widespread pain, chronic low back pain, and chronic pelvic pain. Chronic pain is often associated with fatigue, sleep disturbances, cognitive deficits, and depression. The duration of subacute pain is from a day up to 90 days and includes DOMS, plantar fasciitis, and sickle cell anemia.[40,188-190]

Physical activity benefits chronic pain, sleep, cognitive function, and physical function. It tends to reduce the economic impact of chronic illness through improvements in overall well-being, independence, and reduced healthcare seeking and workplace absenteeism. Overall health benefits occur regardless of whether physical activity is accomplished via low intensity physical activities of daily living, or higher intensity exercise associated with cardiovascular fitness. Since no single modality provides overwhelming symptomatic relief for chronic pain, a combination of pharmacological and nonpharmacological therapies often is most effective.[40,170]

In recent years, it has become apparent that reduction of physical inactivity may have a greater impact on risk of chronic pain than adhering to physical activity recommendations. Physical inactivity or sedentary behavior is ubiquitous at all ages, rendering many chronic diseases once thought to be confined to older populations increasingly common in younger age groups. Further, the sedative action of opioid use contributes to physical inactivity although this factor has not been quantified. But in elderly adults, each additional daily hour of inactivity is estimated to produce 46 percent greater odds of disability including chronic pain to adversely affect activities of daily living. Daily bursts of moderate-vigorous physical activity as recommended by the AHA do not negate the harms of long, continuous hours of sedentary behavior exemplified by prolonged uninterrupted sitting. Minimizing the daily hours spent sitting emerges as the most important factor for both primary and secondary prevention of chronic diseases along with capability of slowing disease progression.[40,191] Interrupting prolonged sitting every 20-60 min by arising from a chair and walking about for 2-3 min prevents endothelial dysfunction and minimizes oxidative stress, contributing factors to chronic pain.[184,192] However, adherence to breaking up sitting time with intermittent walking is a behavioral change that poses a major challenge to both nonaddicted and opioid-addicted individuals. Usage of JD during uninterrupted sitting is a partial solution to physical inactivity without a behavioral change but not a substitute for physical activity.[49]

In 2010, estimated annual costs related to chronic pain were $560-635 billion in combined medical costs, lost earnings, disability, and lost productivity. The most common chronic pain conditions in the United States and the leading global causes of disability of most countries in 2015 were low back and neck pain, osteoarthritis, and headache. The costs of chronic pain of arthritis in the United States were over $189 billion annually. Chronic pain from arthritis is present in more than 22 percent of adults and in nearly half of adults older than 65 years. Furthermore, 24-58 percent of adults with arthritis are physically inactive.[40]

PAIN RELIEF OF α2 ADRENOCEPTOR AGONISTS

In 1970s, drugs belonging to this class were found to provide pain relief, sedation, anxiolytic, and antihypertensive effects without side effects of euphoria and addiction. Clonidine and lofexidine examples of these drugs were approved by FDA for treatment of hypertension but not for opioid addition. Subsequently, it was discovered that they also inhibited symptoms of sudden opioid withdrawal related to the attendant large outflow of norepinephrine into the circulation. As an off-label application, clonidine and lofexidine decreased plasma norepinephrine levels as measured by elevation of its MHPG metabolite.[172] About 25 years later, another drug of this class, dexmedetomidine, was utilized off-label to suppress opioid withdrawal symptoms in infants.[164,193,194] α2 adrenoceptors agonists have varied degrees of antinociception but require presence of phosphorylated eNOS for pain relief.[162,195] JD increases physical activity as measured by increased oxygen consumption (unpublished observations) which increases release of NO with potential to aid in all stages of opioid addiction through up-regulation of eNOS.[49,63] α2 adrenoceptor agonists like clonidine, lofexidine, and dexmedetomidine have the qualitative profile for symptomatic treatment of both chronic pain and opioid addiction in large part by suppressing endogenous norepinephrine levels.[172] The latter is accomplished through increased NO bioavailability derived from eNOS.

Repeated opioid intake leads to complex adaptations in the brain and the gastrointestinal system, that has mu opioid receptors which contribute to diarrhea, nausea, and vomiting during withdrawal. Once OUD or physical dependence is recognized and the patient requests or consents to treatment, a long-term treatment strategy must be defined since it is a chronic disorder that often requires long-term or even life-long treatment. Management of acute withdrawal is the first step during opioid discontinuation or tapering of dose and its frequency. For patients on short-acting opioids, withdrawal symptoms emerge within 18-24 h of the first missed dose. Failure to promptly manage them may cause patients to abandon their recovery attempt at the outset. Detailed discussion of treatment of OUD after the early phase of opioid withdrawal is beyond the scope of this review because of the multifactorial considerations.[196] α2- adrenoceptor agonists such as clonidine are the mainstay of nonopioid support since they specifically target the constellation of symptoms generated by opioid withdrawal-induced noradrenergic hyperactivity. Unfortunately, a dose regimen for clonidine or related drugs has not been established owing due to lack of FDA guidance. The maximum daily doses of clonidine range from 0.9 to 1.35 mg divided over various dosing schedules. For severe withdrawal symptoms, much higher doses may be required repeated as often as hourly if needed by a clonidine-experienced physician to get anxiety and other withdrawal symptoms quickly controlled.[196] Here, experience is necessary because two variables are being altered during the same time period, the native opioid dose, and the α2 adrenoceptor agonist which also has its own share of side-effects.

JD offers an evidenced-based holistic approach for treatment of concurrent opioid addiction and pain. This NO-based generating technology has potential as a stand-alone solution or an adjunct to current pharmacological and nonpharmacological therapies. Administration of the low risk, JD can be begun anytime during tapering or withdrawal of opioids where only the dose and frequency of administration of the opioid addictive drug is varied. JD is devoid of side-effects and can be safely given two to three times a day for 30-60 min each time or at more frequent intervals and lengthier times. Since JD produces effective antinociception while inhibiting norepinephrine activity, it has potential to make a major impact in control of opioid addiction by attention to both pain and addiction.

Nonpharmacological approaches have been recommended for treatment of chronic pain that include increase of physical activity, cognitive behavioral therapy, movement therapies, and acupuncture but do not address the issue of elevated norepinephrine levels. With exception of acupuncture, these measures require behavioral changes that pose issues with adherence. The effects of acupuncture on chronic pain relief are small and independent of placement of the needles between acupuncture points and nonpoints.

Therapies once considered "alternative" such as mindfulness meditation, yoga, relaxation, and movement therapies (Tai Chi, Qigong) provide minimal to no relief in the case of chronic back pain.[197-199]

Opioid effectiveness for pain management has stood the test of time, but its usage has been hampered by unwanted pharmacological effects of craving and euphoria, physical dependence and addiction,

sedation, impaired cognition, severe constipation, respiratory depression, and lethal overdose. As yet, there has not been any opioids discovered or synthesized with minimal or absent addicting properties and solely analgesic effects.

SELECTED CHRONIC AND SUBACUTE PAIN CONDITIONS WITH RISK OF OPIOID USE DISORDER

Successful management of both addiction and chronic pain requires healthy endothelial function and/ or improvement of endothelial dysfunction. The latter is often associated with an unhealthy lifestyle focused on factors contributing to hypertension, cardiovascular diseases, and type 2 diabetes such as (1) poor nutrition, (2) inadequate physical activity, (3) smoking, (4) obesity, and (5) excessive alcohol consumption. Simultaneous correction of all five of these adverse lifestyle behaviors is achieved by less than 2 percent of American adult. This indicates the difficulty in adhering to a healthy lifestyle and consequent need for effortless interventions like JD. Unlike recommendations by governmental and nongovernmental bodies for physical activity, guidance for reducing physical inactivity have not yet been addressed.[30,200,201] The effortless intervention during inadequate physical inactivity with the GENTLE JOGGER addresses one of the unhealthy lifestyle considerations. The beneficial effect of NO as antinociceptive in selected clinical situations while applying the motion platform rather than opioids is summarized below.

Osteoarthritis

Osteoarthritis (OA) is the most common degenerative joint disease, that occurs in more than 25 percent of the population over 18 years. The etiology of OA includes joint injury, obesity, aging, and heredity. Because the molecular mechanisms involved in OA initiation and progression remain poorly understood, there are no current interventions to restore degraded cartilage or decelerate disease progression. OA is the most prevalent joint disease associated with pain and disability. It is expected that 25 percent of the adult population, or more than 50 million people in the United States, will suffer from OA by 2020 and that OA will be a major cause of morbidity and physical limitation among individuals over the age of 40 years major clinical symptoms include chronic pain, joint instability, stiffness, and radiographic joint space narrowing.[202]

In a clinical comparison of opioid and nonopioid drugs for relief of pain in osteoarthritis, therapy comprised the following. In the opioid group, immediate-release morphine, oxycodone, or hydrocodone/acetaminophen is administered while for the nonopioid group, acetaminophen (paracetamol), or a NSAID was utilized. The primary outcome was pain-related function (brief pain inventory (BPI) interference scale) over 12 months and the main secondary outcome was pain intensity (BPI severity scale). It was found that treatment with opioids was not superior to treatment with nonopioid drugs for improving pain-related function over 12 months. Such results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis.[203] Conventional nonpharmacologic treatments such as weight loss and exercise support the use of these treatments in patients with knee osteoarthritis.[204] The effect of exercise varies according to the type of exercise and target outcome. Aerobic or mind-body exercise might be best for pain and function improvements. Strengthening and flexibility/skill exercises might be effective for multiple outcomes.[205]

There is evidence that in cultured chondrocytes the addition of exogenous NO may inhibit proinflammatory activation by preventing the nuclear localization of the transcription factor nuclear factor-κB. Under some conditions, exogenous NO can stimulate collagen synthesis in cultured rat fibroblasts and human tendon cells. The protective roles of NO in multiple cell types, along with the opposing activities in cultured chondrocytes, suggest that NO may play additional protective roles in chondrocyte function.[206]

WBPA and JD have two attributes with potential to alleviate chronic pain associated with osteoarthritis, eg, increased physical activity and antinociception related to an increase of NO bioavailability. In confirmation of this assertion, eight patients with osteoarthritis of the hips and/or knees were treated with WBPA for 45 min administered 5 days a week for 2 weeks. The SF36v2™ health-related quality of life (HR-QOL) questionnaire was administered prior to treatment and on the last day, and scores were compared between the 2 days. Statistical improvements after treatment with WBPA were observed in three of the eight categories of the SF26v2: role physical (RP), bodily pain (BP), and vitality (VT).

Prior to WBPA administration, all three values were significantly reduced compared to normative

values. Improvement after WBPA for osteoarthritis included Role Physical (RF), Bodily Pain (BP), and Vitality (VT). The improvement for the preceding measures exceeded the mean normal values for such measures. Thus, treatment with WBPA for 2 weeks significantly improved vitality, relieved pain and improved role physical in osteoarthritis. (Sackner MA, Adams, JA: Whole body periodic acceleration relieves pain and improves vitality in chronic pain conditions. *Pain Management* 81, 2010 unpublished abstract). In patients with osteoarthritic chronic pain in whom opioids can be justified for preservation of a satisfactory QoL, utilization of JD has potential to reduce opioid dosage.

Fibromyalgia

Fibromyalgia affects up to 15 million Americans and 3.6 percent the world population, is more prevalent in females than males (9:1 ratio) and is usually diagnosed between ages of 20 and 50. Its major symptom is chronic widespread pain with multiple tender points. Fatigue, morning stiffness, and poor sleep quality are associated symptoms. The cause and etiology are not known but there is evidence of increased oxidative stress, chronic inflammation, and decreased blood flow. Pain appears to be centrally mediated with inappropriate heightened pain processing.

The basis for increased oxidative stress and chronic inflammation accompanying physical inactivity in general as well as in patients with fibromyalgia has been investigated in the al-Andalus Project.[207] This project was designed to discriminate between presence or absence of fibromyalgia in patients by determining their ability to perform a specific set of physical fitness tests, such as arm curl, handgrip strength, 30-s chair stand, back scratch, and 6-min walk. The study group consisted of 566 fibromyalgia women and 249 healthy control women as well as 24 fibromyalgia men and 56 healthy control men in southern Spain.

Segura-Jimenez, et al.[207] investigated the amount of time spent in sedentary behavior, mostly involving uninterrupted sitting, in patients with fibromyalgia using accelerometers.

Fibromyalgia patients took fewer steps/day compared to the control subjects. Only 16 percent of these patients walked at least 10,000 steps/day compared with 45 percent of control subjects.

Women who constituted most of the patients with fibromyalgia spent a far greater time in sedentary behaviors and were less physically active than their age-matched controls. In a study of 1,700 adults with fibromyalgia, it was found that opioids were inferior to nonopioid analgesics for pain relief.[208]

We investigated the effects of WBPA in fibromyalgia patients using the Fibromyalgia Impact Questionnaire (FIQ) as the primary endpoint, a disease-specific measure that assesses subjects' perception of their physical function, pain, fatigue, stiffness, depression, anxiety, and overall well-being. Nineteen fibromyalgia patients who received WBPA were treated in sessions lasting 45 min, 5 days a week for 4 weeks, totaling 20 treatments. As the primary outcome measure, the favorable change of Fibromyalgia Impact Questionnaire as well as pain score between baseline and week 4 for WPBA was within the range of pharmacotherapies including pregabalin, the most widely prescribed drug in the United States for fibromyalgia.[80,209] Secondary outcomes of the preceding study included (1) brief fatigue inventory (BFI) score, (2) BPI score, (3) morning stiffness, (4) patients' satisfaction with information questionnaire, (5) self-rating depression scale (SDS), and (6) self-rating anxiety scale (SAS). With exception of SDS that showed no significant change, all the others showed statistical improvement most marked for relief of morning stiffness.[80,210-215]

Peripheral arterial disease

Peripheral arterial disease (PAD) accounts for approximately 20 percent of the 35 million total yearly hospitalizations in the United States.[216] The prevalence of PAD in the United States has not been precisely reported but has been estimated at approximately 15 million adults over age 40 years. The limb manifestations of PAD induce considerable suffering related to intermittent claudication, characterized as exertional leg pain that limits walking distance. Current recommended medical therapies that reduce these lower extremity symptoms have been limited to structured exercise and oral administration of cilostazol. Revascularization by endovascular intervention or surgical reconstruction treats lifestyle-limiting claudication if patients are unresponsive to such medical therapies. Lower extremity revascularization with endovascular approaches has undergone a dramatic increase in use but there are significant risks, and durability may be limited, especially in infra-inguinal disease. The mechanisms that lead to

intermittent claudication in PAD are complex and include reduced limb perfusion, systemic inflammation, oxidative stress and endothelial dysfunction, impaired angiogenesis, reduced microcirculatory flow, and skeletal muscle dysfunction.[217] These abnormalities are potentially minimized or reversed by administration of WBPA or JD.

Intermittent claudication (IC) is marked by reproducible pain affecting muscles of the lower extremities that begins and increases with activity and resolves with rest. The clinical goals of IC management include increasing walking distance and improving QoL. In addition, two drugs have been approved by FDA for treatment of IC, eg, oral cilostazol and pentoxifylline. In 239 patients with IC and moderate severity of PAD, baseline walking distance at baseline was 237m. After 16 weeks of orally administered cilostazol and 12 h after the last dose, walking distance increased 47 percent over the baseline obtained 16 weeks earlier.[218]

Structured exercise improves walking distance in PAD through multiple effects on both vascular and skeletal muscle function including reversal of endothelial dysfunction and reduction of oxidative stress.[219] A patient-centered approach combining medical treatment, exercise intervention, and selective use of revascularization can reduce limb symptoms and improve QoL. The required level of exercise intensity remains elusive but asking patients to walk to near-maximal pain limits adherence to an exercise program owing to their exposure to episodic pain and discomfort.[220]

Critical limb ischemia (CLI), a subset of PAD, is marked by persistent ischemic pain at rest, tissue loss, or gangrene and hypoperfusion of the lower extremity. Approximately 1 percent to 3 percent of patients or up to about 450,000 PAD patients yearly have concurrent CLI. However, with increasing life expectancy and high prevalence of such risk factors as type 2 diabetes, obesity, and sedentary lifestyle, these numbers are likely to increase in the future. CLI is associated with significant mortality, morbidity, increased utilization of health care resources, decreased QoL, immobility, amputation, and ultimately death.[221] Mortality rates as high as 20 percent within 6 months from diagnosis and exceeding 50 percent at 5 years have been reported for CLI, whereas 1-year mortality rates in nonrevascularizable, so-called no-option CLI patients range from 10 percent to 40 percent. The high mortality rates exceed those for every other form of occlusive cardiovascular disease, including symptomatic coronary artery disease (CAD) and reflect the systemic atherosclerotic burden associated with CLI. Besides poor survival rates, prognosis with respect to limb preservation in CLI patients is markedly reduced particularly in no-option CLI patients, where 6-month major amputation rates range from 10 percent to 40 percent.[222] Clearly, there is a high priority need for other medical therapies for these conditions.

One potential PAD therapy is WBPA with its capability of improving endothelial dysfunction and reducing oxidative stress.[65] Using WPBA technology in a study of six patients with severe PAD, the mean baseline pain-free, walking distance on an inclined treadmill distance was 57 m and the maximum walking distance 93 m. After WPBA was administered 40 min 5 days a week for 5 weeks (25 treatments), the pain free walking distance increased 15 percent and maximal walking distance 21 percent.[75] The minimal improvement of walking distance with WPBA might have been due to the low baseline walking distance that suggests a high degree of PAD severity. In another study of WBPA in patients with PAD treated one or 7 days there was a significant increase of skin blood flow to the lower extremities.[69] A clinical trial of JD administered twice daily in PAD is warranted in a home environment.

In 18 of 34 patients with severe PAD, high-pressure, intermittent pneumatic compression (HPIPC) was applied to the foot and calf 60 min twice daily for 16 weeks versus standard care that consisted of walking for 20 min twice daily for 16 weeks. HPIPC delivered bilateral compression pressures of 120 mm Hg. Cycle times provided sequential compression for 4 seconds followed by a 16-second rest period, resulting in a 20-second cycle or 3 cycles per minute. The primary endpoint was peak walking time (PWT), defined as time to maximally tolerated claudication pain. At 4 weeks, the percent change from baseline in PWT did not vary significantly between treatment groups, viz., 18 percent for HPIC and 17 percent for standard care. After 8 weeks, the percent change in PWT for the HPIPC group was 41 percent compared to 32 percent for the group receiving standard care ($p > 0.05$). At the 16-week time point the percent change from baseline in PWT was significantly different between treatment arms 36 percent for the standard care group and 55 percent for the HPIPC group receiving ($p < 0.05$).[223] Therefore, the daily, duration of treatment for HPIPC and the lengthy time period of 16 weeks to achieve significant improvement limit its clinical utility.[224]

External counterpulsation (ECP) technology consists of an apparatus enclosing a programable air pump that inflates a garment which compresses the lower half of the body with each heartbeat such that a pulse is added to the natural pulse in the circulation, thereby doubling the number of pulses. This process enhances shear stress to the endothelium that increases blood flow and improves endothelial function. If ECP is administered to patients with PAD, high pressures up to 300 mmHg attendant with ECP can cause hypoperfusion of the already ischemic limb. As a remedy, Buschmann and associates modified the standard 3-cuff inflation to 2-cuffs wrapped around the hip and thighs and applied pressures from 120-160 mmHg. They called this technology "individual shear rate therapy (ISRT)."[224] Both the initial claudication distance (ICD) and absolute claudication distance (ACD) measurements were obtained by treadmill walking tests at baseline and after 10, 20, and 30 h of ISRT in 14 patients with PAD. The ICD was defined as walking distance without claudication pain. The ACD was walking distance with the most bearable claudication pain. ICD increased after 10 h, 20 h, and 30 h of ISRT compared to baseline conditions 93 to 155m ((67 percent); 229m (146 percent), and 280m (201 percent), respectively).

Similarly, ACD increased after 10 h, 20 h, and 30 h of ISRT compared to baseline (168 to 237 (41 percent), 328 (95 percent), and 447 (168 percent). These results were better than the 25 treatment WBPA trial summarized above possibly because of more severe PAD as evidenced by the low baseline walking distance in the WPBA investigation.

A retrospective study of the Premier Healthcare Database 2009-2015 was performed in 51,000 patients which assessed in-hospital complications, mortality, and hospitalization costs in 976 patients with drug abuse disorder who underwent lower extremity bypass for PAD. The majority of drugs were cannabis (38.5 percent), followed by opioids (21.5 percent) and cocaine (14.5 percent). Patients with a history of drug use/misuse were at higher risk of developing complications during longer hospital stays which were associated with higher costs. In addition, drug users were found to have higher risk of concomitant major amputations compared to nondrug users (2.0 percent versus 0.9 percent).[225]

DELAYED ONSET OF MUSCLE SORENESS (DOMS)

Exercise-induced muscle damage commonly occurs after bouts of unaccustomed eccentric, high-intensity, or long-duration exercise. The latter can also result in delayed perception of skeletal-muscle discomfort or pain termed DOMS that involves soreness, decreased strength, localized swelling, stiffness, and reduced range of motion. It occurs 24-48 h after the exercise bout and is accompanied by increased serum creatine kinase (CK) activity. Depending upon intensity of the exercise bout, symptoms and signs can last at least 96 h accompanied by slowed times of short-distance runs and/ or reduced strength of the exercised segment. An efficacious method to hasten recovery from DOMS would enhance athletic performance on subsequent days and rapidly return the individual to unimpeded activities of daily living. With regard to soccer, a period of 72 h postmatch play is not long enough to completely recover from DOMS and varies among individuals.[226]

DOMS may be produced in (1) upper extremity sports activities, eg, baseball pitching, fast cricket bowlers, overhead football throwing, windmill softball pitching, volleyball serve and spike, and tennis serve and volley, boxing, wrestling, (2) back sports activities, eg, rowing canoeing, weight lifting, (3) lower extremity sports activities, eg, endurance running, basketball, soccer, football, rugby. ice hockey, vigorous dancing, downhill running, mountain climbing & descending, cross country skiing, and (4) occupational activities, eg, manual laborers, military infantry, and forestry workers. There has not been an effective method to significantly hasten recovery from DOMS. Such methods include ice-water immersion, stretching, anti-inflammatory drugs, ultrasound, transcutaneous electric nerve stimulation, massage, compression garments, acupuncture, hyperbaric oxygen therapy, opioids (Tramadol), billberry juice, whole body vibration, exercise, and oral antioxidants. With regard to the latter, meta-analysis of 50 studies which included a total of 1089 participants (961 were male and 128 were female) with an age range of 16-55 years was performed. All studies used an antioxidant dosage higher than the recommended daily amount. High-dose antioxidant supplementation did not result in a clinically relevant reduction of muscle soreness after exercise of up to 6 h or at 24, 48, 72, and 96 h after exercise.[227]

The failure of the preceding methods to hasten recovery from DOMS is not surprising since they have not targeted its pathophysiology. Lopez and associates used downhill treadmill running elicit eccentric exercise (EE) induced muscle damage in mice, and applied WBPA daily for 10 days after the initial EE bout (day 0). Every 2 days during the

WBPA treatment course starting at day 0, intracellular Ca2+ and Na+ concentrations and membrane potential (as indicators of intracellular ion dysfunction) were assessed in vivo in gastrocnemius muscle from the anesthetized mice. EE significantly increased intracellular Ca2+ and Na+, CK, TNF-α, MCP-1, IL-6, and IL-10, all of which peaked on day 2 with the exception of IL-10 and declined slowly over 10 days recovery. WBPA post-EE reduced elevated intracellular Ca2+ and Na+ values toward control values after 6 days of WBPA thereby hastening recovery from simulated DOMS. It also accelerated normalization of CK, TNF-α, MCP-1, and IL-6 while further increasing IL-10 concentrations. The NO synthase inhibitor, L-NG-nitroarginine methyl ester, administered in drinking water before EE and maintained throughout the treatment course, was sufficient to abrogate the salutary effects of WBPA post-EE. Thus, WBPA is the first effective therapeutic strategy to accelerate muscle recovery after EE-induced skeletal muscle injury, as indicated by a faster normalization of all the studied parameters. It also is the basis for the hastened recovery with WBPA from DOMS after EE in young men.[70,188]

NO news is good news

In the early 1980s, NO was just another toxic gaseous molecule, one on a lengthy list of environmental pollutants found in unsavory haunts such as cigarette smoke and smog. Destroyer of ozone, suspected carcinogen, and precursor of acid rain, this gas had a bad reputation. But starting in the late 1980s it was discovered that this sometime poison was a fundamental and most important player in everyday healthy living. In 1992, NO was deemed Molecule of the Year by Science magazine who remarked "A startlingly simple molecule unites neuroscience, physiology, and immunology and revises scientists' understanding of how cells communicate and defend themselves." In 1998, the Nobel Prize in Physiology or Medicine was jointly awarded to Robert F. Furchgott, Louis J. Ignarro, and Ferid Murad for their discoveries concerning "nitric oxide as a signaling molecule in the cardiovascular system." In 1980, 39 scientific papers were published on NO and from that point until today, over 165,000 publications dealing with NO have made their way into the scientific literature. From its identity as a noxious air pollutant in the early 1980s to emergence as a potential savior in the current opioid epidemic, the reputation of NO has undergone a remarkable positive transformation.

Nitric oxide released into the circulation as a gaseous molecule with the motion platform or the GENTLE JOGGER is metabolized in vivo within a few seconds by combination with heme in the red blood cell.[228] Therefore, indirect means such as flow mediated dilatation to demonstrate increased NO in vivo as with the motion platform or GENTLE JOGGER must be employed.[146,229] Recently, metabolites of NO have come under investigation that can be administered orally to produce cyclic guanosine-3',5'-monophophate (cGMP), that transduces many physiological effects of gaseous NO.[230] However, such oral alternatives are dependent on drug distribution kinetics and currently expensive. This is not the case for the GENTLE JOGGER which is not limited by distribution kinetics owing to vascular shear stress to endothelium throughout the circulation.

DISCLOSURE

I have read the journal's policy and the authors of this manuscript have the following competing interests:

MAS is President of Sackner Wellness Products LLC and owns 80% of the latter. He holds a patent for Gentle Jogger® a passive simulated jogging device. JAA is Scientific Director for Sackner Wellness Products LLC and owns 20 percent of the latter. He is a co-patent holder for Gentle Jogger®. VB is a part time study coordinator and employee of Sackner Wellness Products LLC. She does not have ownership interest in Sackner Wellness Products. JRL is a Research Scientist consultant with Sackner Wellness Products LLC. He does not have ownership interest in Sackner Wellness Products. This study was funded by Sackner Wellness Products LLC. This does not alter our adherence to the Journal policies on sharing data and materials.

Marvin A. Sackner, MD, Emeritus Director of Medical Services, Mt Sinai Medical Center of Greater Miami, Miami Beach, Florida.

Jose R. Lopez, MD, Research Associate, Mt Sinai Medical Center of Greater Miami, Miami Beach, Florida.

Veronica Banderas, BA TR, Research Associate, Sackner Wellness Products LLC, Miami, Florida.

Jose A. Adams. MD, Chief, Division of Neonatology, Mt Sinai Medical Center of Greater Miami, Miami Beach, Florida.

REFERENCES

1. Carise D, Dugosh KL, McLellan AT, et al.: Prescription OxyContin abuse among patients entering addiction treatment. *Am J Psychiatry.* 2007; 164(11): 1750-1756.

2. deShazo RD, Johnson M, Eriator I, et al.: Backstories on the US Opioid Epidemic: Good intentions gone bad, an industry gone rogue, and watch dogs gone to sleep. *Am J Med.* 2018; 131(6): 595-601.

3. Prekupec MP, Mansky PA, Baumann MH: Misuse of novel synthetic opioids: A deadly new trend. *J Addict Med.* 2017; 11(4): 256-265.

4. Schaefer CP, Tome ME, Davis TP. The opioid epidemic: A central role for the blood brain barrier in opioid analgesia and abuse. *Fluids Barriers CNS.* 2017; 14(1): 32.

5. Schuckit MA: Treatment of opioid-use disorders. *N Engl J Med.* 2016; 375(16): 1596-1597.

6. Zawilska JB: An expanding world of novel psychoactive substances: Opioids. *Front Psychiatry.* 2017; 8: 110.

7. Thornton JD, Goyat R, Dwibedi N, et al.: Health-related quality of life in patients receiving long-term opioid therapy: A systematic review with meta-analysis. *Qual Life Res.* 2017; 26(8): 1955-1967.

8. Dillie KS, Fleming MF, Mundt MP, et al.: Quality of life associated with daily opioid therapy in a primary care chronic pain sample. *J Am Board Fam Med.* 2008; 21(2): 108-117.

9. Krebs E, Kerr T, Wood E, et al.: Characterizing long-term health related quality of life trajectories of individuals with opioid use disorder. *J Subst Abuse Treat.* 2016; 67: 30-37.

10. Rajaratnam R, Sivesind D, Todman M, et al.: The aging methadone maintenance patient: Treatment adjustment, long-term success, and quality of life. *J Opioid Manag.* 2009; 5(1): 27-37.

11. Sakhuja A, Sztajnkrycer M, Vallabhajosyula S, et al.: National trends and outcomes of cardiac arrest in opioid overdose. *Resuscitation.* 2017; 121: 84-89.

12. Chen Q, Larochelle MR, Weaver DT, et al.: Prevention of prescription opioid misuse and projected overdose deaths in the United States. *JAMA Netw Open.* 2019; 2(2): e187621.

13. Cicero TJ, Ellis MS: The prescription opioid epidemic: A review of qualitative studies on the progression from initial use to abuse. *Dialogues Clin Neurosci.* 2017; 19(3): 259-269.

14. Van Zee A: The promotion and marketing of oxycontin: Commercial triumph, public health tragedy. *Am J Public Health.* 2009; 99(2): 221-227.

15. Page MG, Kudrina I, Zomahoun HTV, et al.: Relative frequency and risk factors for long-term opioid therapy following surgery and trauma among adults: A systematic review protocol. *Syst Rev.* 2018; 7(1): 97.

16. Younger JW, Chu LF, D'Arcy NT, et al.: Prescription opioid analgesics rapidly change the human brain. *Pain.* 2011; 152(8): 1803-1810.

17. Hines LA, Lynskey M, Morley KI, et al.: The relationship between initial route of heroin administration and speed of transitionto daily heroin use. *Drug Alcohol Rev.* 2017; 36(5): 633-638.

18. Bohnert ASB, Ilgen MA: Understanding links among opioid use, overdose, and suicide. *N Engl J Med.* 2019; 380(1): 71-79.

19. Nock NL, Minnes S, Alberts JL: Neurobiology of substance use in adolescents and potential therapeutic effects of exercise for prevention and treatment of substance use disorders. *Birth Defects Res.* 2017; 109(20): 1711-1729.

20. McCabe SE, Veliz PT, Boyd CJ, et al.: A prospective study of nonmedical use of prescription opioids during adolescence and subsequent substance use disorder symptoms in early midlife. *Drug Alcohol Depend.* 2019; 194: 377-385.

21. McCarty D, Priest KC, Korthuis PT: Treatment and prevention of opioid use disorder: challenges and opportunities. *Annu Rev Public Health.* 2018; 39: 525-541.

22. Stein MD, Santiago Rivera OJ, Anderson BJ, et al.: Perceived need for depression treatment among persons entering inpatient opioid detoxification. *Am J Addict.* 2017; 26(4): 395-399.

23. Weiss RD, Rao V: The prescription opioid addiction treatment study: What have we learned. *Drug Alcohol Depend.* 2017; 173(Suppl 1): S48-S54.

24. McDermott KA, Griffin ML, Connery HS, et al.: Initial response as a predictor of 12-week buprenorphine-naloxone treatment response in a prescription opioid-dependent population. *J Clin Psychiatry.* 2015; 76(2): 189-194.

25. Muller AE, Skurtveit S, Clausen T: Many correlates of poor quality of life among substance users entering treatment are not addiction-specific. *Health Qual Life Outcomes.* 2016; 14: 39.

26. De Maeyer J, Vanderplasschen W, Lammertyn J, et al.: Current quality of life and its determinants among opiate-dependent individuals five years after starting methadone treatment. *Qual Life Res.* 2011; 20(1): 139-150.

27. Jones JD, Vogelman JS, Luba R, et al.: Chronic pain and opioid abuse: Factors associated with health-related quality of life. *Am J Addict.* 2017; 26(8): 815-821.

28. Akazawa N, Ra SG, Sugawara J, et al.: Influence of aerobic exercise training on post-exercise responses of aortic pulse pressure and augmentation pressure in postmenopausal women. *Front Physiol.* 2015; 6: 268.

29. Booth FW, Roberts CK, Thyfault JP, et al.: Role of inactivity in chronic diseases: Evolutionary insight and pathophysiological mechanisms. *Physiol Rev.* 2017; 97(4): 1351-1402.

30. Bouchard C, Blair SN, Katzmarzyk PT: Less sitting, more physical activity, or higher fitness? *Mayo Clin Proc.* 2015; 90(11): 1533-1540.

31. Finni T, Haakana P, Pesola AJ, et al.: Exercise for fitness does not decrease the muscular inactivity time during normal daily life. *Scand J Med Sci Sports.* 2014; 24(1): 211-219.

32. Watson KB, Carlson SA, Gunn JP, et al.: Physical inactivity among adults aged 50 years and older—United States, 2014. *MMWR Morb Mortal Wkly Rep.* 2016; 65(36): 954-958.

33. Cheval B, Tipura E, Burra N, et al.: Avoiding sedentary behaviors requires more cortical resources than avoiding physical activity: An EEG study. *Neuropsychologia.* 2018; 119: 68-80.

34. Bardo MT, Compton WM: Does physical activity protect against drug abuse vulnerability? *Drug Alcohol Depend.* 2015; 153: 3-13.

35. Ghitza UE, Zhai H, Wu P, et al.: Role of BDNF and GDNF in drug reward and relapse: A review. *Neurosci Biobehav Rev.* 2010; 35(2): 157-171.

36. Weiss RD: Adherence to pharmacotherapy in patients with alcohol and opioid dependence. *Addiction.* 2004; 99(11): 1382-1392.

37. Litz M, Leslie D: The impact of mental health comorbidities on adherence to buprenorphine: A claims based analysis. *Am J Addict.* 2017; 26(8): 859-863.

38. Surbhi S, Graetz I, Wan JY, et al.: The effect of opioid use and mental illness on chronic disease medication adherence in superutilizers. *J Manag Care Spec Pharm.* 2018; 24(3): 198-207.

39. Dahlhamer J, Lucas J, Zelaya C, et al:. Prevalence of chronic pain and high-impact chronic pain among adults—United States, 2016. *MMWR Morb Mortal Wkly Rep.* 2018; 67(36): 1001-1006.

40. Ambrose KR, Golightly YM: Physical exercise as non-pharmacological treatment of chronic pain: Why and when. *Best Pract Res Clin Rheumatol.* 2015; 29(1): 120-130.

41. Manhapra A, Becker WC: Pain and addiction: An integrative therapeutic approach. *Med Clin North Am.* 2018; 102(4): 745-763.

42. Bart G: Maintenance medication for opiate addiction: The foundation of recovery. *J Addict Dis.* 2012; 31(3): 207-225.

43. Dugosh K, Abraham A, Seymour B, et al.: A systematic review on the use of psychosocial interventions in conjunction with medications for the treatment of opioid addiction. *J Addict Med.* 2016; 10(2): 93-103.

44. Pergolizzi JV, Jr, Annabi H, Gharibo C, et al.: The role of lofexidine in management of opioid withdrawal. *Pain Ther.* 2018; 8(1): 67-78.

45. Babatunde OO, Jordan JL, Van der Windt DA, et al.: Effective treatment options for musculoskeletal pain in primary care: A systematic overview of current evidence. *PLoS One.* 2017; 12(6): e0178621.

46. Da Silva Santos R, Galdino G: Endogenous systems involved in exercise-induced analgesia. *J Physiol Pharmacol.* 2018; 69(1): 3-13.

47. Senba E, Kami, K: A new aspect of chronic pain as a lifestyle-related disease. *Neurobiol Pain.* 2017; 1: 6-15.

48. Sackner MA, Gummels E, Adams JA: Nitric oxide is released into circulation with whole-body, periodic acceleration. *Chest.* 2005; 127(1): 30-39.

49. Sackner MA, Patel S, Adams JA: Changes of blood pressure following initiation of physical inactivity and after external addition of pulses to circulation. *Eur J Appl Physiol.* 2019; 119(1): 201-211.

50. Sackner MA: Whole-body, periodic acceleration relieves pain and improves vitality in chronic pain conditions (Abstract). International symposium on nitric oxide, cytokines and inflammation. 2004.

51. Colledge F, Vogel M, Dursteler-Macfarland K, et al.: A pilot randomized trial of exercise as adjunct therapy in a heroin-assisted treatment setting. *J Subst Abuse Treat.* 2017; 76: 49-57.

52. Weinstock J, Wadeson HK, VanHeest JL: Exercise as an adjunct treatment for opiate agonist treatment: Review of the current research and implementation strategies. *Subst Abuse.* 2012; 33(4): 350-360.

53. Weinstock J, Farney MR, Elrod NM, et al.: Exercise as an adjunctive treatment for substance use disorders: Rationale and intervention description. *J Subst Abuse Treat.* 2017; 72: 40-47.

54. Hutcheson IR, Griffith TM: Release of endothelium-derived relaxing factor is modulated both by frequency and amplitude of pulsatile flow. *Am J Physiol.* 1991; 261(1 Pt 2): H257-H262.

55. Adams JA, Moore JE, Jr, Moreno MR, et al.: Effects of periodic body acceleration on the in vivo vasoactive response to N-omega-nitro-L-arginine and the in vitro nitric oxide production. *Ann Biomed Eng.* 2003; 31(11): 1337-1346.

56. Abraham WM, Ahmed A, Serebriakov I, et al.: Whole-body periodic acceleration modifies experimental asthma in sheep. *Am J Respir Crit Care Med.* 2006; 174(7): 743-752.

57. Adams JA, Bassuk J, Wu D, et al.: Survival and normal neurological outcome after CPR with periodic Gz acceleration and vasopressin. *Resuscitation.* 2003; 56(2): 215-221.

58. Adams JA, Bassuk JA, Arias J, et al.: Acute effects of "delayed postconditioning" with periodic acceleration after asphyxia induced shock in pigs. *Pediatr Res.* 2008; 64(5): 533-537.

59. Adams JA, Mangino MJ, Bassuk J, et al.: Regional blood flow during periodic acceleration. *Crit Care Med.* 2001; 29(10): 1983-1988.

60. Adams JA, Mangino MJ, Bassuk J, et al.: Hemodynamic effects of periodic G(z) acceleration in meconium aspiration in pigs. *J Appl Physiol (1985).* 2000; 89(6): 2447-2452.

61. Adams JA, Uryash A, Bassuk J, et al.: Biological basis of neuroprotection and neurotherapeutic effects of whole body periodic acceleration (pGz). *Med Hypotheses.* 2014; 82(6): 681-687.

62. Adams JA, Wu H, Bassuk JA, et al. Periodic acceleration (pGz) prior to whole body ischemia reperfusion injury provides early cardioprotective preconditioning. *Life Sci.* 2010; 86(19-20): 707-715.

63. Adams JA, Wu H, Bassuk JA, et al.: Periodic acceleration (pGz) acutely increases endothelial and neuronal nitric oxide synthase expression in endomyocardium of normal swine. *Peptides.* 2009; 30(2): 373-377.

64. Altamirano F, Perez CF, Liu M, et al.: Whole body periodic acceleration is an effective therapy to ameliorate muscular dystrophy in mdx mice. *PLoS One.* 2014; 9(9): e106590.

65. Uryash A, Bassuk J, Kurlansky P, et al.: Antioxidant properties of whole body periodic acceleration (pGz). *PLoS One.* 2015; 10(7): e0131392.

66. Uryash A, Bassuk J, Kurlansky P, et al.: Non-invasive technology that improves cardiac function after experimental myocardial infarction: Whole body periodic acceleration (pGz). *PLoS One.* 2015; 10(3): e0121069.

67. Martinez A, Arias J, Bassuk JA, et al.: Adrenomedullin is increased by pulsatile shear stress on the vascular endothelium via periodic acceleration (pGz). *Peptides.* 2008; 29(1): 73-78.

68. Martinez-Murillo R, Serrano J, Fernandez AP, et al.: Whole-body periodic acceleration reduces brain damage in a focal ischemia model. *Neuroscience.* 2009; 158(4): 1390-1396.

69. Rokutanda T, Izumiya Y, Miura M, et al.: Passive exercise using whole-body periodic acceleration enhances blood supply to ischemic hindlimb. *Arterioscler Thromb Vasc Biol.* 2011; 31(12): 2872-2880.

70. Lopez JR, Mijares A, Kolster J, et al.: Whole body periodic acceleration improves muscle recovery after eccentric exercise. *Med Sci Sports Exerc.* 2016; 48(8): 1485-1494.

71. Sakaguchi M, Fukuda S, Shimada K, et al.: Preliminary observations of passive exercise using whole body periodic acceleration on coronary microcirculation and glucose tolerance in patients with type 2 diabetes. *J Cardiol.* 2012; 60(4): 283-287.

72. Adams JA, Pastuszko P, Uryash A, et al.: Whole Body Periodic Acceleration (pGz) as a non-invasive preconditioning strategy for pediatric cardiac surgery. *Med Hypotheses.* 2018; 110: 144-149.

73. Fujita M, Sasayama S: Coronary collateral growth and its therapeutic application to coronary artery disease. *Circ J.* 2010; 74(7): 1283-1289.

74. Fukuda S, Shimada K, Kawasaki T, et al.: "Passive exercise" using whole body periodic acceleration: effects on coronary microcirculation. *Am Heart J.* 2010; 159(4): 620-626.

75. Kohler M, Amann-Vesti BR, Clarenbach CF, et al.: Periodic whole body acceleration: A novel therapy for cardiovascular disease. *Vasa.* 2007; 36(4): 261-266.

76. Matsumoto T, Fujita M, Tarutani Y, et al.: Whole-body periodic acceleration enhances brachial endothelial function. *Circ J.* 2008; 72(1): 139-143.

77. Miyamoto S, Fujita M, Inoko M, et al.: Effect on treadmill exercise capacity, myocardial ischemia, and left ventricular function as a result of repeated whole body periodic acceleration with heparin pretreatment in patients with angina pectoris and mild left ventricular dysfunction. *Am J Cardiol.* 2011; 107(2): 168-174.

78. Sackner MA, Gummels E, Adams JA: Effect of moderate-intensity exercise, whole- body periodic acceleration, and passive cycling on nitric oxide release into circulation. *Chest.* 2005; 128(4): 2794-2803.

79. Sackner MA, Gummels EM, Adams JA: Say NO to fibromyalgia and chronic fatigue syndrome: An alternative and complementary therapy to aerobic exercise. *Med Hypotheses.* 2004; 63(1): 118-123.

80. Sackner MA: Does fibromyalgia sit in a chair? Symptomatic relief with a simulated jogging device. *Fibromyalgia*: Open Access. 2017; 2(1): 1-5.

81. Kitada M, Ogura Y, Koya D: The protective role of Sirt1 in vascular tissue: its relationship to vascular aging and atherosclerosis. *Aging* (Albany NY). 2016; 8(10): 2290-2307.

82. Palatini P, Mos L, Mormino P, et al.: Blood pressure changes during running in humans: The "beat" phenomenon. *J Appl Physiol (1985).* 1989; 67(1): 52-59.

83. Sackner MA: Is awareness of obesity and type 2 diabetes from physical inactivity in the home and workplace well recognized. *Adv Obes Weight Manag Control.* 2017; 6(6): 158-162.

84. Adams JA, Patel S, Lopez JR, et al.: The effects of passive simulated jogging on short-term heart rate variability in a heterogeneous group of human subjects. *J Sports Med (Hindawi Publ Corp).* 2018; 2018: 4340925.

85. Caspersen CJ, Powell KE, Christenson GM: Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Rep.* 1985; 100(2): 126-131.

86. Di Francescomarino S, Sciartilli A, Di Valerio V, et al.: The effect of physical exercise on endothelial function. *Sports Med.* 2009; 39(10): 797-812.

87. Ando J, Yamamoto K: Vascular mechanobiology: Endothelial cell responses to fluid shear stress. *Circ J.* 2009; 73(11): 1983-1992.

88. Adams JA, Uryash A, Lopez JR, et al.: Whole body periodic acceleration improves survival and microvascular leak in a murine endotoxin model. *PLoS One.* 2019; 14(1): e0208681.

89. Giovannitti JA, Jr, Thoms SM, Crawford JJ: Alpha-2 adrenergic receptor agonists:a review of current clinical applications. *Anesth Prog.* 2015; 62(1): 31-39.

90. Wang D, Wang Y, Wang Y, et al.: Impact of physical exercise on substance use disorders: A meta-analysis. *PLoS One.* 2014; 9(10): e110728.

91. Guthold R, Stevens GA, Riley LM, et al.: Worldwide trends in insufficient physical activity from 2001 to 2016: A pooled analysis of 358 population-based surveys with 1.9 million participants. *Lancet Glob Health.* 2018; 6(10): e1077-e1086.

92. Henson J, Dunstan DW, Davies MJ, et al.: Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes. *Diabetes Metab Res Rev.* 2016; 32(Suppl 1): 213-220.

93. Buckley JP, Hedge A, Yates T, et al.: The sedentary office: An expert statement on the growing case for change towards better health and productivity. *Br J Sports Med.* 2015; 49(21): 1357-1362.

94. Dempsey PC, Larsen RN, Dunstan DW, et al.: Sitting less and moving more: implications for hypertension. *Hypertension.* 2018; 72(5): 1037-1046.

95. Larsen RN, Kingwell BA, Sethi P, et al.: Breaking up prolonged sitting reduces resting blood pressure in overweight/obese adults. *Nutr Metab Cardiovasc Dis.* 2014; 24(9): 976-982.

96. Higgins ST. Editorial: 2nd special issue on behavior change, health, and health disparities. *Prev Med.* 2015; 80: 1-4.

97. Wilms B, Ernst B, Thurnheer M, et al.: Correction factors for the calculation of metabolic equivalents (MET) in overweight to extremely obese subjects. *Int J Obes (Lond).* 2014; 38(11): 1383-1387.

98. Burns J, Forde C, Dockrell S: Energy expenditure of standing compared to sitting while conducting office tasks. *Hum Factors.* 2017; 59(7): 1078-1087.

99. Tyton TN, Scott HM, Horswill CA: Metabolic rate during a cognitive vigilance challenge at alternative workstations. *J Occup Environ Med.* 2018; 60(6): e307-e311.

100. Padilla J, Fadel PJ: Prolonged sitting leg vasculopathy: Contributing factors and clinical implications. *Am J Physiol Heart Circ Physiol.* 2017; 313(4): H722-H728.

101. Restaino RM, Walsh LK, Morishima T, et al.: Endothelial dysfunction following prolonged sitting is mediated by a reduction in shear stress. *Am J Physiol Heart Circ Physiol.* 2016; 310(5): H648-H653.

102. Laina A, Stellos K, Stamatelopoulos K: Vascular ageing: Underlying mechanisms and clinical implications. *Exp Gerontol.* 2018; 109: 16-30.

103. Morishima T, Restaino RM, Walsh LK, et al.: Prolonged sitting-induced leg endothelial dysfunction is prevented by fidgeting. *Am J Physiol Heart Circ Physiol.* 2016; 311(1): H177-H182.

104. Hsieh HJ, Liu CA, Huang B, et al.: Shear-induced endothelial mechanotransduction: The interplay between reactive oxygen species (ROS) and nitric oxide (NO) and the pathophysiological implications. *J Biomed Sci.* 2014; 21: 3.

105. Adams V, Linke A, Krankel N, et al.: Impact of regular physical activity on the NAD(P)H oxidase and angiotensin receptor system in patients with coronary artery disease. *Circulation.* 2005; 111(5): 555-562.

106. Bangalore S, Toklu B, Gianos E, et al.: Optimal systolic blood pressure target after SPRINT: Insights from a network meta-analysis of randomized trials. *Am J Med.* 2017; 130(6): 707-719.

107. Muntner P, Whelton PK, Woodward M, et al.: A comparison of the 2017 American College of Cardiology/American Heart Association Blood Pressure Guideline and the 2017 American Diabetes Association Diabetes and Hypertension Position Statement for US Adults With Diabetes. *Diabetes Care.* 2018; 41(11): 2322-2329.

108. Fiuza-Luces C, Garatachea N, Berger NA, et al.: Exercise is the real polypill. *Physiology (Bethesda).* 2013; 28(5): 330-358.

109. Johnson BD, Mather KJ, Wallace JP: Mechanotransduction of shear in the endothelium: Basic studies and clinical implications. *Vasc Med.* 2011; 16(5): 365-377.

110. Seals DR, Walker AE, Pierce GL, et al.: Habitual exercise and vascular ageing. *J Physiol.* 2009; 587(Pt 23): 5541-5549.

111. Toda N: Age-related changes in endothelial function and blood flow regulation. *Pharmacol Ther.* 2012; 133(2): 159-176.

112. Toda N, Nakanishi-Toda M: How mental stress affects endothelial function. *Pflugers Arch.* 2011; 462(6): 779-794.

113. Donato AJ, Machin DR, Lesniewski LA: Mechanisms of dysfunction in the aging vasculature and role in age-related disease. *Circ Res.* 2018; 123(7): 825-848.

114. Zheng C, Liu Z: Vascular function, insulin action, and exercise: An intricateinterplay. *Trends Endocrinol Metab.* 2015; 26(6): 297-304.

115. Lobelo F, Rohm Young D, Sallis R, et al.: Routine assessment and promotion of physical activity in healthcare settings: A scientific statement from the American Heart Association. *Circulation.* 2018; 137(18): e495-e522.

116. Duvivier B, Bolijn JE, Koster A, et al.: Reducing sitting time versus adding exercise: Differential effects on biomarkers of endothelial dysfunction and metabolic risk. *Sci Rep.* 2018; 8(1): 8657.

117. Walker AE, Kaplon RE, Pierce GL, et al.: Prevention of age-related endothelial dysfunction by habitual aerobic exercise in healthy humans: Possible role of nuclear factor kappaB. *Clin Sci (Lond).* 2014; 127(11): 645-654.

118. Doukas N: Older adults prescribed methadone: A review of the literature across the life span from opiate initiation to methadone maintenance treatment. *Curr Drug Abuse Rev.* 2014; 7(3): 165-173.

119. Reece AS, Hulse GK: Impact of opioid pharmacotherapy on arterial stiffnessand vascular ageing: Cross-sectional and longitudinal studies. *Cardiovasc Toxicol.* 2013; 13(3): 254-266.

120. Reece AS, Hulse GK: Impact of lifetime opioid exposure on arterial stiffness and vascular age: Cross-sectional and longitudinal studies in men and women. *BMJ Open.* 2014; 4(6): e004521.

121. Reece AS, Hulse GK: Duration of opiate exposure as a determinant of arterial stiffness and vascular age in male opiate dependence: A longitudinal study. *J Clin Pharm Ther.* 2014; 39(2): 158-167.

122. Gfroerer J, Penne M, Pemberton M, et al.: Substance abuse treatment need among older adults in 2020: The impact of the aging baby-boom cohort. *Drug Alcohol Depend.* 2003; 69(2): 127-135.

123. Maillard P, Mitchell GF, Himali JJ, et al.: Effects of arterial stiffness on brain integrity in young adults from the Framingham heart study. *Stroke.* 2016; 47(4): 1030-1036.

124. van Sloten TT, Mitchell GF, Sigurdsson S, et al.: Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: Cross-sectional findings from the AGES-Reykjavik Study. *J Psychiatry Neurosci.* 2016; 41(3): 162-168.

125. van Sloten TT, Protogerou AD, Henry RM, et al.: Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: A systematic review and meta-analysis. *Neurosci Biobehav Rev.* 2015; 53: 121-130.

126. Fukuda D, Yoshiyama M, Shimada K, et al.: Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease. *Heart.* 2006; 92(6): 759-762.

127. Gould KL, Johnson NP: Coronary physiology beyond coronary flow reserve in microvascular angina: JACC state-of-the-art review. *J Am Coll Cardiol.* 2018; 72(21): 2642-2662.

128. Tritakis V, Tzortzis S, Ikonomidis I, et al.: Association of arterial stiffness with coronary flow reserve in revascularized coronary artery disease patients. *World J Cardiol.* 2016; 8(2): 231-239.

129. Esmaeili Nadimi A, Pour Amiri F, Sheikh Fathollahi M, et al.: Opium addiction as an independent risk factor for coronary microvascular dysfunction: A case-control study of 250 consecutive patients with slow-flow angina. *Int J Cardiol.* 2016; 219: 301-307.

130. Marinescu MA, Loffler AI, Ouellette M, et al.: Coronary microvascular dysfunction, microvascular angina, and treatment strategies. *JACC Cardiovasc Imaging.* 2015; 8(2): 210-220.

131. Ahmadi-Abhari S, Sabia S, Shipley MJ, et al.: Physical activity, sedentary behavior, and long-term changes in aortic stiffness: The Whitehall II study. *J Am Heart Assoc.* 2017; 6(8).

132. Ashor AW, Lara J, Siervo M, et al.: Effects of exercise modalities on arterial stiffness and wave reflection: A systematic review and meta- analysis of randomized controlled trials. *PLoS One.* 2014; 9(10): e110034.

133. Kohn JC, Lampi MC, Reinhart-King CA: Age-related vascular stiffening: Causes and consequences. *Front Genet.* 2015; 6: 112.

134. Isabelle M, Simonet S, Ragonnet C, et al.: Chronic reduction of nitric oxide level in adult spontaneously hypertensive rats induces aortic stiffness similar to old spontaneously hypertensive rats. *J Vasc Res.* 2012; 49(4): 309-318.

135. Costantino S, Paneni F, Cosentino F: Ageing, metabolism and cardiovasculardisease. *J Physiol.* 2016; 594(8): 2061-2073.

136. Hayashi T, Matsui-Hirai H, Miyazaki-Akita A, et al.: Endothelial cellular senescence is inhibited by nitric oxide: implications in atherosclerosis associated with menopause and diabetes. *Proc Natl Acad Sci USA.* 2006; 103(45): 17018-17023.

137. Foreman DL, Sanders M, Bloor CM: Total and regional cerebral blood flow during moderate and severe exercise in miniature swine. *J Appl Physiol.* 1976; 40(2): 191-195.

138. Stebbins CL, Symons JD: Role of angiotensin II in hemodynamic responses to dynamic exercise in miniswine. *J Appl Physiol* (1985). 1995; 78(1): 185-190.

139. Denier N, Gerber H, Vogel M, et al.: Reduction in cerebral perfusion after heroin administration: A resting state arterial spin labeling study. *PLoS One.* 2013; 8(9): e71461.

140. Jellinger KA: Pathogenesis and treatment of vascular cognitive impairment. *Neurodegener Dis Manag.* 2014; 4(6): 471-490.

141. Kurita GP, de Mattos Pimenta CA, Braga PE, et al.: Cognitive function in patients with chronic pain treated with opioids: Characteristics and associated factors. *Acta Anaesthesiol Scand.* 2012; 56(10): 1257-1266.

142. Puca AA, Carrizzo A, Ferrario A, et al.: Endothelial nitric oxide synthase, vascular integrity and human exceptional longevity. *Immun Ageing.* 2012; 9(1): 26.

143. Cheng GL, Zeng H, Leung MK, et al.: Heroin abuse accelerates biological aging: A novel insight from telomerase and brain imaging interaction. *Transl Psychiatry.* 2013; 3: e260.

144. Cunha-Oliiveira TC, Rego AC, et al.: Oxidative stress and drugs of abuse: An update. Mini-Rev Org Chem. 2013; 10: 1-14.

145. Lam CF, Liu YC, Tseng FL, et al.: High-dose morphine impairs vascular endothelial function by increased production of superoxide anions. *Anesthesiology.* 2007; 106(3): 532-537.

146. Takase B, Hattori H, Tanaka Y, et al. Acute effect of whole-body periodic acceleration on brachial flow-mediated vasodilatation assessed by a novel semi-automatic vessel chasing UNEXEF18G system. *J Cardiovasc Ultrasound.* 2013; 21(3): 130-136.

147. Salvemini D: Peroxynitrite and opiate antinociceptive tolerance: A painful reality. *Arch Biochem Biophys.* 2009; 484(2): 238-244.

148. Muscoli C, Cuzzocrea S, Ndengele MM, et al.: Therapeutic manipulation of peroxynitrite attenuates the development of opiate-induced antinociceptive tolerance in mice. *J Clin Invest.* 2007; 117(11): 3530-3539.

149. Matsuda M, Huh Y, Ji RR: Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth.* 2019; 33(1): 131-139.

150. Shen CH, Tsai RY, Wong CS: Role of neuroinflammation in morphine tolerance: Effect of tumor necrosis factor-alpha. *Acta Anaesthesiol Taiwan.* 2012; 50(4): 178-182.

151. Allen SJ, Dawbarn D: Clinical relevance of the neurotrophins and their receptors. *Clin Sci (Lond).* 2006; 110(2): 175-191.

152. Peregud DI, Yakovlev AA, Stepanichev MY, et al.: Expression of BDNF and TrkB phosphorylation in the rat frontal cortex during morphine withdrawal are NO dependent. *Cell Mol Neurobiol.* 2016; 36(6): 839-849.

153. Carnicella S, Ron D: GDNF—A potential target to treat addiction. *Pharmacol Ther.* 2009; 122(1): 9-18.

154. Marie C, Pedard M, Quirie A, et al.: Brain-derived neurotrophic factor secreted by the cerebral endothelium: A new actor of brain function? *J Cereb Blood Flow Metab.* 2018; 38(6): 935-949.

155. Monnier A, Prigent-Tessier A, Quirie A, et al.: Brain-derived neurotrophic factor of the cerebral microvasculature: A forgotten and nitric oxide-dependent contributor of brain-derived neurotrophic factor in the brain. *Acta Physiol (Oxf).* 2017; 219(4): 790-802.

156. Lopez JR, Uryash A, Kolster J, et al.: Enhancing endogenous nitric oxide by whole body periodic acceleration elicits neuroprotective effects in dystrophic neurons. *Mol Neurobiol.* 2018; 55(11): 8680-8694.

157. Pang PT, Teng HK, Zaitsev E, et al.: Cleavage of proBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science.* 2004; 306(5695): 487-491.

158. Maglione MA, Raaen L, Chen C, et al.: Effects of medication assisted treatment(MAT) for opioid use disorder on functional outcomes: A systematic review. *J Subst Abuse Treat.* 2018; 89: 28-51.

159. Sofuoglu M, DeVito E, Carroll K: Pharmacological and behavioral treatment of opioid use disorder. *PRCP Adv.* 2018: 12.

160. Toce MS, Chai PR, Burns MM, et al.: Pharmacologic treatment of opioid use disorder: A review of pharmacotherapy, adjuncts, and toxicity. *J Med Toxicol.* 2018; 14(4): 306-322.

161. Shipton EA, Shipton EE, Shipton AJ: A review of the opioid epidemic: What do we do about it? *Pain Ther.* 2018; 7(1): 23-36.

162. Feldman J, Fellmann L, Bousquet P: The central hypotensive effect induced by alpha 2-adrenergic receptor stimulation is dependent on endothelial nitric oxide synthase. *J Hypertens.* 2008; 26(5): 1033-1036.

163. Fresquez-Chavez KR, Fogger S: Reduction of opiate withdrawal symptoms with use of clonidine in a county jail. *J Correct Health Care.* 2015; 21(1): 27-34.

164. Gold MS, Redmond DE, Jr., Kleber HD. Clonidine blocks acute opiate-withdrawal symptoms. *Lancet.* 1978; 2(8090): 599-602.

165. Gold MS, Redmond DE, Jr., Kleber HD: Noradrenergic hyperactivity in opiate withdrawal supported by clonidine reversal of opiate withdrawal. *Am JPsychiatry.* 1979; 136(1): 100-102.

166. Nunes EV, Gordon M, Friedmann PD, et al.: Relapse to opioid use disorder after inpatient treatment: Protective effect of injection naltrexone. *J Subst Abuse Treat.* 2018; 85: 49-55.

167. Salarian A, Kadkhodaee M, Zahmatkesh M, et al.: Opioid use disorder induces oxidative stress and inflammation: The attenuating effect of methadone maintenance treatment. *Iran J Psychiatry.* 2018; 13(1): 46-54.

168. Cury Y, Picolo G, Gutierrez VP, et al.: Pain and analgesia: The dual effect of nitric oxide in the nociceptive system. *Nitric Oxide.* 2011; 25(3): 243-254.

169. Strauch B, Herman C, Dabb R, et al.: Evidence-based use of pulsed electromagnetic field therapy in clinical plastic surgery. *Aesthet Surg J.* 2009; 29(2): 135-143.

170. Tick H, Nielsen A, Pelletier KR, et al.: Evidence-based nonpharmacologic strategies for comprehensive pain care: The consortium pain task force white paper. *Explore (NY).* 2018; 14(3): 177-211.

171. Doughty B, Morgenson D, Brooks T: Lofexidine: A newly FDA-approved, nonopioid treatment for opioid withdrawal. *Ann Pharmacother.* 2019: 53(7): 746-753.

172. Charney DS, Redmond DE, Jr, Galloway MP, et al.: Naltrexone precipitated opiate withdrawal in methadone addicted human subjects: evidence for noradrenergic hyperactivity. *Life Sci.* 1984; 35(12): 1263-1272.

173. Gertler R, Brown HC, Mitchell DH, et al.: Dexmedetomidine: A novelsedative-analgesic agent. *Proc (Bayl Univ Med Cent).* 2001; 14(1): 13-21.

174. Li HJ, Li CJ, Wei XN, et al.: Dexmedetomidine in combination with morphine improves postoperative analgesia and sleep quality in elderly patients after open abdominal surgery: A pilot randomized control trial. *PLoS One.* 2018; 13(8): e0202008.

175. Peng K, Zhang J, Meng XW, et al.: Optimization of postoperative intravenous patient-controlled analgesia with opioid-dexmedetomidine combinations: An updated meta-analysis with trial sequential analysis of randomized controlled trials. *Pain Physician.* 2017; 20(7): 569-596.

176. de Moura RS, Rios AA, Santos EJ, et al.: Role of the NO-cGMP pathway in the systemic antinociceptive effect of clonidine in rats and mice. *Pharmacol Biochem Behav.* 2004; 78(2): 247-253.

177. Dobrucki LW, Cabrera CL, Bohr DF, et al.: Central hypotensive action of clonidine requires nitric oxide. *Circulation.* 2001; 104(16): 1884-1886.

178. Sy GY, Bruban V, Bousquet P, et al.: Nitric oxide and central antihypertensive drugs: one more difference between catecholamines and imidazolines. *Hypertension.* 2001; 37(2): 246-249.

179. Hser YI, Mooney LJ, Saxon AJ, et al.: Chronic pain among patients with opioid use disorder: Results from electronic health records data. *J Subst Abuse Treat.* 2017; 77: 26-30.

180. Hung AL, Lim M, Doshi TL: Targeting cytokines for treatment of neuropathic pain. *Scand J Pain.* 2017; 17: 287-293.

181. Anastas T, Colpitts K, Ziadni M, et al.: Characterizing chronic pain in late adolescence and early adulthood: Prescription opioids, marijuana use, obesity, and predictors for greater pain interference. *Pain Rep.* 2018; 3(6): e700.

182. Carter S, Hartman Y, Holder S, et al.: Sedentary behavior and cardiovascular disease risk: Mediating mechanisms. *Exerc Sport Sci Rev.* 2017; 45(2): 80-86.

183. Gratas-Delamarche A, Derbre F, Vincent S, et al.: Physical inactivity, insulin resistance, and the oxidative-inflammatory loop. *Free Radic Res.* 2014; 48(1): 93-108.

184. Thosar SS, Bielko SL, Mather KJ, et al.: Effect of prolonged sitting and breaks in sitting time on endothelial function. *Med Sci Sports Exerc.* 2015; 47(4): 843-849.

185. Salvemini D, Little JW, Doyle T, et al.: Roles of reactive oxygen and nitrogen species in pain. *Free Radic Biol Med.* 2011; 51(5): 951-966.

186. Volkow ND, McLellan AT: Opioid abuse in chronic pain—misconceptions and mitigation strategies. *N Engl J Med.* 2016; 374(13): 1253-1263.

187. Dunn KE, Brooner RK, Clark MR: Severity and interference of chronic pain in methadone-maintained outpatients. *Pain Med.* 2014; 15(9): 1540-1548.

188. Serravite DH, Perry A, Jacobs KA, et al.: Effect of whole-body periodic acceleration on exercise-induced muscle damage after eccentric exercise. *Int J Sports Physiol Perform.* 2014; 9(6): 985-992.

189. Valentin GH, Pilegaard MS, Vaegter HB, et al.: Prognostic factors for disability and sick leave in patients with subacute non-malignant pain: A systematic review of cohort studies. *BMJ Open.* 2016; 6(1): e007616.

190. Al-Boloushi Z, Lopez-Royo MP, Arian M, et al.: Minimally invasive non-surgical management of plantar fasciitis: A systematic review. *J Bodyw Mov Ther.* 2019; 23(1): 122-137.

191. Dunlop DD, Song J, Arnston EK, et al.: Sedentary time in US older adults associated with disability in activities of daily living independent of physical activity. *J Phys Act Health.* 2015; 12(1): 93-101.

192. Dempsey PC, Sacre JW, Larsen RN, et al.: Interrupting prolonged sitting with brief bouts of light walking or simple resistance

activities reduces resting blood pressure and plasma noradrenaline in type 2 diabetes. *J Hypertens.* 2016; 34(12): 2376-2382.

193. Rasouli J, Lekhraj R, White NM, et al.: Attenuation of interleukin-1beta by pulsed electromagnetic fields after traumatic brain injury. *Neurosci Lett.* 2012; 519(1): 4-8.

194. Uryash A, Wu H, Bassuk J, et al.: Preconditioning with periodic acceleration (pGz) provides second window of cardioprotection. *Life Sci.* 2012; 91(5-6): 178-185.

195. Aronov S, Ben-Abraham R, Givati-Divshi D, et al.: Cerebroventricular injection of clonidine causes analgesia mediated by a nitrogen pathway. *Drug Metabol Drug Interact.* 2005; 21(1): 55-66.

196. Kosten TR, Baxter LE: Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. *Am J Addict.* 2019; 28(2): 55-62.

197. Teut M, Knilli J, Daus D, et al.: Qigong or yoga versus no intervention in older adults with chronic low back pain-a randomized controlled trial. *J Pain.* 2016; 17(7): 796-805.

198. Teut M, Ullmann A, Ortiz M, et al.: Pulsatile dry cupping in chronic low back pain—A randomized three-armed controlled clinical trial. *BMC Complement Altern Med.* 2018; 18(1): 115.

199. Ma SX: Nitric oxide signaling molecules in acupoints: Toward mechanisms of acupuncture. *Chin J Integr Med.* 2017; 23(11): 812-815.

200. Barbaresko J, Rienks J, Nothlings U: Lifestyle indices and cardiovascular disease risk: A meta-analysis. *Am J Prev Med.* 2018; 55(4): 555-564.

201. Fang J, Moore L, Loustalot F, et al.: Reporting of adherence to healthy lifestyle behaviors among hypertensive adults in the 50 states and the District of Columbia, 2013. *J Am Soc Hypertens.* 2016; 10(3): 252-262.

202. Chen D, Shen J, Zhao W, et al.: Osteoarthritis: Toward a comprehensive understanding of pathological mechanism. *Bone Res.* 2017; 5: 16044.

203. Krebs EE, Gravely A, Nugent S, et al.: Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial. *JAMA.* 2018; 319(9): 872-882.

204. Lee YC, Shmerling RH: The benefit of nonpharmacologic therapy to treat symptomatic osteoarthritis. *Curr Rheumatol Rep.* 2008; 10(1): 5-10.

205. Goh SL, Persson MSM, Stocks J, et al.: Relative efficacy of different exercises for pain, function, performance and quality of life in knee and hip osteoarthritis: Systematic review and network meta-analysis. *Sports Med.* 2019; 49(5): 743-761.

206. Abramson SB: Nitric oxide in inflammation and pain associated with osteoarthritis. *Arthritis Res Ther.* 2008; 10(Suppl 2): S2.

207. Segura-Jimenez V, Borges-Cosic M, Soriano-Maldonado A, et al.: Association of sedentary time and physical activity with pain, fatigue, and impact of fibromyalgia: The al-Andalus study. *Scand J Med Sci Sports.* 2017; 27(1): 83-92.

208. Peng X, Robinson RL, Mease P, et al.: Long-term evaluation of opioid treatment in fibromyalgia. *Clin J Pain.* 2015; 31(1): 7-13.

209. Argoff CE, Emir B, Whalen E, et al.: Pregabalin improves pain scores in patients with fibromyalgia irrespective of comorbid osteoarthritis. *Pain Med.* 2016; 17(11): 2100-2108.

210. Boers M, Buttgereit F, Saag K, et al.: What is the relationship between morning symptoms and measures of disease activity in patients with rheumatoid arthritis? *Arthritis Care Res (Hoboken).* 2015; 67(9): 1202-1209.

211. Cleeland CS, Ryan KM: Pain assessment: Global use of the brief pain inventory. *Ann Acad Med Singapore.* 1994; 23(2): 129-138.

212. Martins JC. Patients' satisfaction with information on disease and morbidity. *Rev Lat Am Enfermagem.* 2009; 17(3): 335-340.

213. Mendoza TR, Wang XS, Cleeland CS, et al.: The rapid assessment of fatigue severity in cancer patients: Use of the Brief Fatigue Inventory. *Cancer.* 1999; 85(5): 1186-1196.

214. Zung WW: A self-rating depression scale. *Arch Gen Psychiatry.* 1965; 12: 63-70.

215. Zung WW: A rating instrument for anxiety disorders. *Psychosomatics.* 1971; 12(6): 371-379.

216. Fanari Z, Weintraub WS: Cost-effectiveness of medical, endovascular and surgical management of peripheral vascular disease. *Cardiovasc Revasc Med.* 2015; 16(7): 421-425.

217. Hamburg NM, Creager MA: Pathophysiology of intermittent claudication in peripheral artery disease. *Circ J.* 2017; 81(3): 281-289.

218. Money SR, Herd JA, Isaacsohn JL, et al.: Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg.* 1998; 27(2): 267-274; discussion 274-265.

219. Ismaeel A, Brumberg RS, Kirk JS, et al.: Oxidative stress and arterial dysfunction in peripheral artery disease. *Antioxidants (Basel).* 2018; 7(10).

220. McDermott MM: Functional impairment in peripheral artery disease and how to improve it in 2013. *Curr Cardiol Rep.* 2013; 15(4): 347.

221. Agarwal S, Sud K, Shishehbor MH: Nationwide trends of hospital admission and outcomes among critical limb ischemia patients: From 2003-2011. *J Am Coll Cardiol.* 2016; 67(16): 1901-1913.

222. Teraa M, Conte MS, Moll FL, et al.: Critical limb ischemia: Current trends and future directions. *J Am Heart Assoc.* 2016; 5(2).

223. Alvarez OM, Wendelken ME, Markowitz L, et al.: Effect of high-pressure, intermittent pneumatic compression for the treatment of peripheral arterial disease and critical limb ischemia in patients without a surgical option. *Wounds.* 2015; 27(11): 293-301.

224. Buschmann EE, Brix M, Li L, et al.: Adaptation of external counterpulsation based on individual shear rate therapy improves endothelial function and claudication distance in peripheral artery disease. *Vasa.* 2016; 45(4): 317-324.

225. Dakour-Aridi H, Arora M, Nejim B, et al.: Association between drug use and in-hospital outcomes after infrainguinal bypass for peripheral arterial occlusive disease. *Ann Vasc Surg.* 2019; 58: 122-133.

226. Silva JR, Rumpf MC, Hertzog M, et al.: Acute and residual soccer match-related fatigue: A systematic review and meta-analysis. *Sports Med.* 2018; 48(3): 539-583.

227. Ranchordas MK, Rogerson D, Soltani H, et al.: Antioxidants for preventing and reducing muscle soreness after exercise: A cochrane systematic review. *Br J Sports Med.* 2018.

228. Viinikka L: Nitric oxide as a challenge for the clinical chemistry laboratory. *Scand J Clin Lab Invest.* 1996; 56(7): 577-581.

229. Vanhoutte PM, Zhao Y, Xu A, et al.: Thirty years of saying NO: Sources, fate, actions, and misfortunes of the endothelium-derived vasodilator mediator. *Circ Res.* 2016; 119(2): 375-396.

230. Buys ES, Zimmer DP, Chickering J, et al.: Discovery and development of next generation sGC stimulators with diverse multidimensional pharmacology andbroad therapeutic potential. *Nitric Oxide.* 2018; 78: 72-80.