



RESEARCH You Can Use



Stay current on the latest addiction research with executive summaries and analysis provided by Mark Gold, MD.

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NIH Director Affirms Commitment to Basic Science Research

Collins, FS, et al. Basic science: Bedrock of progress. Science Magazine, 351:1405, 2016

Link: <https://www.ncbi.nlm.nih.gov/pubmed/27013720>

NIH-Medline Plus: NIH New Director. Summer 2009 Issue: Volume 4 Number 3 Page 2 <https://medlineplus.gov/magazine/issues/summer09/articles/summer09pg2.html>

In a brief summative letter to the Editor of Science, the Director of the National Institute of Health (NIH) Dr. Francis Collins and colleagues reaffirmed their commitment to basic science as the foundation from which discovery inexorably leads to new theories, translational research and important medical and scientific progress. Dr. Collins knows of what he speaks. Known as the “gene hunter” while at the University of Michigan, Dr. Collins led the Human Genome Project from its inception and has been named to the National Academy of Science, and the Institute of Medicine (IOM). His pedigree speaks volumes of his commitment to basic science.

The crux of the letter responds to concerned critics, that the NIH no longer prioritizes basic science. Citing a decline of applications for basic science projects, Dr. Collins states that the facts tell another story. First of all, correlation is not causation, e.g., fewer submissions for basic scientific research do not mean, nor suggest, that the NIH is less interested in basic science. The fact is, fewer applications are being submitted, which in turn, has led some to erroneously conclude that the NIH is simply not as interested in funding basic scientific research as it has been in the past.

The truth is Dr. Collins and colleagues at NIH have prioritized basic science within its broad portfolio of funded applications, including translational, population, and clinical studies.

For example, NIH has many strategic partnerships with world-class academic institutions and health centers, and wholeheartedly support the translation of basic science research into superior tools and methodologies to bridge current gaps in knowledge, and improve patient care to the degree that will improve our nation’s health. This unprecedented commitment is made possible by awards from the NIH Common Fund and administered by the National Center for Advancing Translational Sciences (NCATS). Bottom line. NIH is, and always has been, a champion for basic scientific research.

Why Does This Matter?

The NIH commitment to translational research is advancing the frontiers of neuroscience, brain disease and developing evidenced-based clinical practice guidelines to address the current public health crisis of addictive disease and other chronic psychiatric disorders.

At present, addiction remains poorly understood when compared to other chronic, life threatening diseases such as diabetes or hypertension. With over 23 million currently addicted adolescents and adults in the U.S., and very limited resources or access to them, most will never receive the treatment they require. The human suffering, mortality and cost of untreated addiction to individuals, families, and to our nation are immeasurable. We are just beginning to understand the genetic and neurobiological mechanisms that drive this chronic illness. Yet funded scientific inquiry is not on par when compared to conditions with similar prevalence and mortality rates. So we applaud the efforts of Dr. Collins and the NIH, as well as its subsidiary organizations such as the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH).



Surgeon General's Call to Action: Addiction is a "Public Health Crisis" in America

Murthy VH.. *Surgeon General's Report on Alcohol, Drugs, and Health* JAMA. 2016 Nov 17. doi: 10.1001/jama.2016.18215
<https://www.ncbi.nlm.nih.gov/pubmed/27854372>

Murthy VH.. *Surgeon General's Report on Alcohol, Drugs, and Health: Viewpoint* JAMA. 2017;317(2):133-134. doi:10.1001/jama.2016.18215JAMA.

In an unprecedented action to "end the public health crisis of addiction" the Office of the Surgeon General released its first ever report on the challenges of ad-diction in America, titled Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health. This well constructed, evidenced based report highlighted the horrors and challenges we face in helping those with sub-stance use disorders. The report cited 5 key areas that must be addressed. They are:

- The Neurobiology of Substance Use, Misuse, and Addiction
- Prevention Programs and Policies
- Early Intervention, Treatment, and Management of Substance Use Disorders
- Recovery: The Many Paths to Wellness
- Health Care Systems and Substance Use Disorders

Moreover, the report unflinchingly addressed the collateral damage done to families and entire communities when this devastating disease is untreated. Accordingly, the report's overarching message is that addictive disease is among the most pressing public health problems in the United States.

Here's why

At present, 21 million Americans age 12 and older have been diagnosed with substance use disorder. Another 2 million remain undiagnosed, bringing the total to 23 million addicts in the U.S. today. To put these numbers in perspective, there are slightly more than people with substance use disorder than with diabetes, and addiction is 1.5 times more prevalent in the U.S. than cancer—any type of cancer. Yet unlike diabetes or cancer, only 1 in 10 of those with substance use disorder receive any type of treatment. The results are disastrous, not only for the individual, but also to his or her family, the community, and to our nation. And it's getting worse. Today 8,000 Americans, most of whom are teens and children, will use an intoxicating, addictive substance for the very first time.

"A moral test for America"

In his accompanying letter to the report, The Surgeon General, Dr. Vivek H Murthy writes:

"We can never forget that the faces of substance use disorders are real people,"...Are we able to live up to that most fundamental obligation we have as human beings: to care for one another?"

While it's not breaking news, the Surgeon General's endorsement for expanding prevention and treatment services in the community, increasing access to treatment, and training more clinicians to recognize and treat substance use disorders is important. The Surgeon General believes that treatment should be integrated into the traditional medical care system, citing the Mental Health Parity and Addiction Equity Act of 2008, mandating payers to reimburse for legitimate treatment modalities, as they would for any other medical condition. Moreover, substance use disorder is a chronic debilitating condition with relapse rates comparable to diabetes, asthma, and hypertension—but here's the big difference. When an asthmatic or diabetic patient relapses, they do not commit crimes or hurt others to self-medicate their symptoms. All the more reason to support prevention, and when that fails, provide addiction medicine and psychiatry treatment with the necessary resources.

Why Does This Matter?

First and foremost, the best available evidence reveals that addiction, officially known as Substance Use Disorder is a multifaceted disease with numerous risk factors from trauma and in utero exposure to genetic hardwiring. Substance use may compromise development and learning and cause measurable changes in the brain's reward, motivation, and mood systems.

Dr. Murphy suggests that more research is needed to "understand the biopsy-chosocial aspects of addiction." In addition, more dedicated classroom and clinical training of physicians and health professionals is desperately needed to diagnose, refer, or treat this disease. And finally, community wide calls to action of all the stakeholders (clinicians, researchers, families, educators, courts and the health care system providers and payers) to work collaboratively toward providing the resources necessary to educate, prevent, and treat this deadly disease.

Suicide Rate is Much Higher Than Previously Reported

Bostwick, JM . et al. Suicide Attempt as a Risk Factor for Completed Suicide: Even More Lethal Than We Knew. AmJPsychiatry 2016; 173:1094–1100; doi: 10.1176/appi.ajp.2016.15070854 Link: <https://www.ncbi.nlm.nih.gov/pubmed/27523496>

Addiction doctors, psychiatrists and other mental health and primary care providers frequently evaluate patients for depression, suicidal ideation, and intent. Experts have long known that previous suicide attempts are the most important factor in predicting future attempts. However, a new study by Bostick and colleagues (2016) reveals that previous research is wrought with methodological limitations (such as convenience sampling) and often overlooked first-attempt (index) deaths. The new findings reveal that deaths by suicide are nearly 60% higher than previously reported.

How did we miss this?

An innovative addition of this latest study may explain the discrepancy-index deaths. During the study period, 81 of the 1,490 enrollees (5.4%) died by suicide. Of the 81 completed suicides, 48 (59.3%) perished on index attempt; of the survivors (81.8%) killed themselves within a year.

Also, firearm deaths have increased but are predominantly categorized as death by suicide. Further, firearms were used in 75% of first attempt fatalities by men. Whereas firearms are used less often by women, the mortality rate, when they are used, is the same as men.

The first take home message is clear. The 12 months following a first suicide attempt is critical, as 80% of the subsequent deaths by suicide occur within this year—and, are strongly associated with the use of a gun. (odds ratio estimate of 140 (95% CI=60-325). The second message is actually good news. Survivors of first attempts were less likely to re-attempt within 12 months when they had a follow-up appointment scheduled upon discharge, even if the appointment was not actually kept. (odds ratio=0.212, 95% CI=0.089-0.507).

As clinicians, these findings are important for several reasons: 1) Suicide prevention efforts should start BEFORE the first attempt, as nearly two-thirds are fatal. 2) The use of a firearms continues to be the most lethal modality in suicides. Accordingly, depression, coupled with easy access to a firearm, is associated with increased mortality by suicide. 3) Follow-up appointments



resulting from a failed suicide attempt should be locked in place prior to discharge from the healthcare facility, and 4). Because the 12 months immediately following a first attempt is critical, aggressive psychiatric care and psychosocial management, including access to treatment prevention resources, are absolutely essential.

Why Does This Matter?

As the concordance rate between depression and substance use disorder is over 50%, addiction professionals must assess and identify depression, past suicide attempts, and current suicidal ideation during any and all treatment events. At present there remains some controversy among addiction professionals regarding the necessity and efficacy of treating co-occurring mental illness during primary addiction treatment. Some argue that once the addiction is managed the depressive symptoms will subside—inferring a causal relationship between addiction and depression. Others believe in a co-occurring model, which asserts that it doesn't matter which came first, both must be treated aggressively. Although we practice amid this tension, we cannot forget that the cost of untreated depression is too high. Suicide is now the second leading cause of death among teens and young adults. The mortality rate of untreated or underrated depression for adults is over 15%.

What should we do? Highly trained addiction medicine doctors and addiction psychiatrists are essential in identification of depression and suicide risk for patients with substance use disorders. More training and innovative treatment modalities for individuals with depression and dual disorders are necessary.

Cannabis Use Causing Alarming Increase in Emergency Hospital Visits and Childhood Poisoning

Zhu H1, Wu LT. Trends and Correlates of Cannabis-involved Emergency Department Visits: 2004 to 2011. *J Addict Med.* 2016 Nov/Dec;10(6):429-436.

Wang, GS, et al. Unintentional Pediatric Exposures to Marijuana in Colorado, 2009-2015. *JAMA Pediatrics*, 2016; e160971 DOI: 10.1001/jamapediatrics.2016.0971

This new epidemiological study looked at trends and correlates of Emergency Department (ED) visits related to cannabis use in the United States. The ED visit rate increased for both cannabis-only use (51 to 73 visits per 100,000; $p < 0.004$) and cannabis-polydrug use (63 to 100 per 100,000; $p < 0.001$) in those aged 12 and older. Of note, the largest increase occurred in adolescents aged 12-17, and among persons who identified as non-Hispanic black. Additionally, the odds of hospitalization increased with older age users, as compared to adolescent admissions. These data suggest a heavier burden to both the patient and to the health care system as a result of increasing cannabis use among older adults. The severity of the "burden" is associated with the prevalence of cannabis use, specific cannabis potency and dose (which is increasing over time), the mode of administration, and numerous individual risk factors. The authors hypothesize that the rise in high-potency cannabis may increase the prevalence of addiction and the need for treatment—which, in turn, can lead to an even higher disease burden and healthcare utilization by

cannabis users. The authors also advocate for frequent screening for cannabis in the ED, and increasing focus and intervention on adolescents and non-Hispanic black patients whom are statistically at higher risk.

Why Does This Matter?

In 2012, Colorado was the first of many states to legalize the sale and recreational use of crude cannabis. The most recent data shows even more unintentional cannabis poisoning of children and ER visits for cannabis induced psychiatric illness, including psychosis, depression and suicide attempts. In addition, the July 25, 2016 JAMA Network Journal Source reported. "The legalization of recreational marijuana in Colorado was associated with both increased hospital visits and cases at a regional poison center because of unintentional exposure to the drug by children." The average rate of marijuana-related visits to the children's hospital has doubled two years after legalization. Moreover, the Regional Poison Center (RPC) reported that since legalization, pediatric marijuana poisoning cases increased more than 5-fold in Colorado.

At present there seems to be no way to avoid the conflict between evidence based medicine and the social and the political movement that is driving public policy regarding cannabis.



Cannabis Abuse and Addiction Related to Increases in Mental Illness and Treatment Admissions

Bloomfield MA et al The effects of 9-tetrahydrocannabinol on the dopamine system. Nature. 2016 Nov 16;539(7629):369-377. doi: 10.1038/nature20153. Link: <https://www.ncbi.nlm.nih.gov/pubmed/27853201>

Behind alcohol, cannabis is the most frequently used recreational drug in the U.S. It is also the second most cited reason for treatment admissions in the U.S., again behind alcohol.

What the best available data reveals

Cannabis is associated with increased risk of mental disorders, including psychosis, depression, suicide attempts, cognitive impairment, interpersonal problems, poor academic performance and amotivation. In Europe, cannabis addiction has now overtaken heroin addiction as the most widely reported reason people seek addiction treatment.

Like all addictive drugs, many of the reinforcing effects of delta 9 THC (the psychoactive constituent of cannabis) are mediated by the dopamine system. Acute crude cannabis administration causes increased dopamine release and neuronal activity which new users experience as pleasurable. Whereas regular

and long-term use is associated with blunting of the dopamine system, which is associated with depression and boredom—and not pleasure. Accordingly, the best available evidence indicates that cannabis, like other addicting drugs, can produce complex, diverse, and potentially long-term degradation of the dopamine system. As a result, the brain's reward thresh-old is elevated, resulting in mood swings, motivational deficits, anhedonia, behavioral problems and of course, addiction.

Why Does This Matter?

The research is clear—cannabis is a harmful, addictive drug. So it is important to re-member that smoking is injection of an addictive drug without a needle. Cigarettes, needles, pipes, spray paint, bongs, vaping, joints, brownies, etc., are simply “drug delivery devices”—or methods to efficiently deliver a psychoactive substance to the brain.

At present, in the U.S., cannabis use disorder ranks second behind alcohol use disorder as the most cited reason for admission to treatment. This is not by accident. Cannabis use, especially among adolescents, causes loss of control and repeated harmful consequences.

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Getting Old, High, and Addicted: Drug Misuse, Abuse and Addiction in the Golden Years

Maree, RD, Et al. *A systematic Review of Opioid and Benzodiazepine Misuse in Older Adults. Am J. Geriatric Psychiatry. 2016 Nov.24(11) 949-963. doi: 10.1016/j.jagp. Epup 2016 June 7*

It is now estimated that 5.7 million Americans age 50 and older will become addicted, and in need of treatment by the year 2020. Using a systematic review and PRISMA guidelines, Maree and colleagues (2016) examined the available evidence on opioid and benzodiazepine prescription patterns, as well as misuse, abuse and addiction among older adults in the U.S. Opioids and benzodiazepines were chosen because of their association with fatal and nonfatal overdoses, as well as the overall high mortality rate associated with these medications.

Opioids and benzodiazepines are commonly prescribed together because of the undesirable side effects associated with opioid use, e.g., insomnia, pain, muscle spasms, anxiety and depression, to name a few. The authors suggest, and we agree, that older adults are likely adjusting their dose without direction or approval from the prescribing physician, while unaware of the adverse reactions and the potential risks associated with their combined use.

This study reviewed publications that included participants age ≥ 65 years. The available evidence germane to substance use disorder was sparse. As our society ages, particularly baby boomers, more cohort studies are needed. The authors recommend better and more frequent screening for drug misuse, particularly in the primary care setting, where aging adults go for medical evaluation, advice and treatment.

Why Does This Matter?

The baby boomers are aging and anecdotal evidence from communities in Florida suggest that the 60s with sex, drugs, and rock n roll are making a comeback. STDs and addictions among these aging boomers is a fact of life in Florida. Skyrocketing mortality among those with opioid use disorder suggests a need for more research and the development of age specific overdose prevention, as well as opioid antagonist or substitution therapy for some across the lifespan. Second, for older adults, changes in liver function is normal, but for drug and alcohol abusers, liver function is often com-promised and thus, related to the increased risk of overdose and accidental death. The article informs professionals of the urgent need for more research and development better age specific prevention and treatment resources, especially those that address the complex health needs of older adults with substance use disorders.



Speed Ages and Kills: Amphetamine Dependence Causes Premature Cardiovascular Disease and Biological Aging

Reece AS, Norman A, Hulse GK Acceleration of cardiovascular-biological age by amphetamine exposure is a power function of chronological age Heart Asia 2017; 9: 30-38. doi: 10.1136/heartasia-2016-010832

New research has confirmed what David Smith and the Haight Asbury pioneers re-reported in the 60s: “speed kills”. Many clinicians have suspected, observed and reported on consequence of amphetamine use and binges for years. Amphetamine, cocaine and the abuse of methamphetamine and ecstasy are associated with premature biological aging that is even more robust than smoking cigarettes. These findings, according to Reese, et al, stood after adjusting for multiple variables, including all known cardiovascular risk factors. Amphetamine users had prematurely aging hearts as measured by arterial stiffness ($P < 0.0001$)

Although the cardiovascular and aging effects associated with certain stimulant drugs are more likely than not a result of chronic use and addiction—a chronic multifaceted brain disease that effects every organ and system in the human body. It is also notable that the use of psycho-stimulants in children with ADHD is not associated with a prematurely aging vasculature. More research is needed.

Why Does This Matter?

The use and abuse of stimulant drugs is a serious public health concern. The fact that these drugs are easily manufactured domestically makes interdiction difficult. As a result, they remain relatively inexpensive, easy to attain and very dangerous.

Because cardiovascular issues are associated with amphetamine abuse and addiction, attaining a detailed, lifelong drug history and systems assessment is critical. In the treatment environment, a thorough and specific drug use evaluation is completed as soon as possible. If amphetamines are a drug of choice, or have been used in the past, a cardiovascular symptom screening is conducted. The screening and examination evaluates for chest pain, shortness of breath, exercise intolerance, PND, orthopnea, edema, palpitations, faintness, loss of consciousness, and claudication. Addressing any positive findings during an evaluation or treatment event is associated with the highest quality patient care.

The Twisted Sisters: Addiction and Suicide

Monnat, S.M. Drugs, Alcohol, and Suicide Represent Growing Share of U.S. Mortality. Carsey School of Public Policy, University of New Hampshire, National Brief 112, Winter, 2017

In a recent paper (2017) University of New Hampshire researcher S.M Monnat reported that suicide rates in the U.S. are increasing at staggering levels, as are deaths from drug and alcohol poisoning. These three combined, suicide + drug poisoning + alcohol poisoning, have increased by an unprecedented 52% between 2000 and 2014, which totals an additional 133,000 deaths.

Why Does This Matter?

We have known for some time that drug and alcohol misuse and abuse and suicide are the leading cause of death among young white males in the U.S. This comprises nearly 50% of all mortality in this cohort. But why?

Both drugs and alcohol target the brain's pleasure and reinforcement systems, primarily through neuronal dopamine signaling. The possibility of neurotoxicity has been discussed by experts for many years, as well as disruption of dopamine signals. Neuroadaptation resulting from substance abuse often results in once pleasurable activities becoming no longer pleasurable. Consequently anhedonia, boredom and prolonged depression is not uncommon among abstinent former users. In addition to the social, familial and legal consequences and stressors, young men (>25 years old), have an undeveloped prefrontal cortex (PFC). The PFC is home to many of our learned and higher human functions. When fully developed, the PFC inhibits impulsiveness, risk taking and solely hedonic driven behavior via dopamine signaling. More emphasis should be placed on the neuroadaptive changes associated with substance use and abuse, and their causal role for addiction, depression and suicidality. Understanding the mechanisms underlying addiction, depression and suicide requires a re-newed commitment to more basic science research.



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Drug Addicts Get Sicker, Age Faster

Bachi K, Sierra S, Volkow ND, Goldstein RZ, Alia-Klein N. Is biological aging accelerated in drug addiction? Curr Opin Behav Sci. 2017 Feb;13:34-39.

Visual observation alone tells much of the story. Methamphetamine addicts often look old, as do cigarette smokers. Drug addicts almost always look older than their non-addicted cohorts. This paper by Bachi, Volkow, et al., suggests that drug-addiction may by itself trigger early onset of age-related disease due, in part, to drug-induced, multi-system toxicity and the high-risk lifestyle associated with trauma, disease and declining health.

The authors identify pathophysiological processes associated with addictive disease and aging including: oxidative stress and cellular aging, inflammation in the periphery and the brain, decreased brain volume and function, and early onset of cardiac, cerebrovascular, kidney, and liver disease.

Why Does This Matter?

This is a very high powered group of national research leaders. The idea that the Director of NIDA, Nora Volkow, has written this paper suggests that the data is robust and accumulating to a level where the authors support the association between drug use and premature aging.

Prevention, as always, is the only 100% successful treatment. Identification of addiction in those with premature morbidity and early mortality seems like too little too late. More research from NIH-NIDA on the early aging phenomenon is needed for everyone, including health professionals.

Obesity Plus Inactivity— A Lose-Lose Proposition

Kravitz AV1, O'Neal TJ2, Friend DM2 Do Dopaminergic Impairments Underlie Physical Inactivity in People with Obesity? Front Hum Neurosci. 2016 Oct 14;10:514. eCollection 2016.

Despite the overwhelming evidence that increased physical activity is associated with cardiovascular health, a sedentary lifestyle continues as the norm for most obese individuals. This self-defeating lifestyle is difficult to understand. So what is going on here?

Our brains are hard wired to preserve energy, even if it means circling around a parking lot waiting for a parking spot near the mall or store entrance.

The lack of effective real world interventions for increasing physical activity levels among obese individuals is confounding because on one hand, increased physical activity is perhaps the most accessible and cost effective disease prevention and intervention modality known. I have often thought that food, sugar, and fat was addicting...and it was too bad exercise was not very reinforcing. For the obese person, exercise may be painful or not possible. The authors tackle this conundrum by suggesting

a lack of understanding of the cellular and molecular mechanisms underlying obesity and the inability for obese people to adhere to a prescribed activity plan. Physical inactivity is associated with functional changes in the basal ganglia, providing a neurobiological explanation for the sedentary lifestyle among obese persons.

Why Does This Matter?

Despite a wide expert consensus that the obese should exercise more, the adherence rate to even prescribed increases of physical activity is nearly null. This study suggests that it is not the patient's fault. We agree. Impairments in dopamine signaling play a role in obesity, and also treatment resistance. Chronic exposure to obesogenic diets has been linked to impairments in dopamine synthesis, release, and receptor function, particularly in the striatum. Striatal dopamine is necessary for various activities, numerous survival functions and, the proper control of movement. By identifying the biological determinants of physical inactivity, we may learn more about more effective strategies for increasing healthy activity in people with and without this disease.

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