Dr. Joseph Frascella

WHY YOU CAN'T "JUST SAY NO": Combatting Drug Addiction is Harder Than You Might Think

THE FRONTAL AREAS OF THE YOUNG BRAIN DEVELOP LAST. THOSE DO THE MORE EXECUTIVE FUNCTION—THE INHIBITORY CONTROL MECHANISM.

by Amy Klein

Drug addiction is a disease, according to the National Institute on Drug Abuse (NIDA), the federal focal point for research on drug abuse and addiction, which has been part of the National Institutes of Health since 1992. NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction. NIDA estimates that substance abuse for illicit drugs, tobacco and alcohol—including health- and crime-related costs and losses in productivity—exceed half a trillion dollars annually. Dr. Joseph Frascella, PhD, director of NIDA's Clinical Neuroscience and Behavioral Research Division, heads a broad drug abuse and addiction program of translational research and research training in clinical neuroscience, human development and behavioral treatment. He discusses how drug addiction changes the brain, why children are particularly vulnerable, and how neuroscience and brain imaging can change what the future holds for treatment.

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BRAIN WORLD: *Prior to your work with drug addiction, you worked with NIDA's pain research program. Why did you get involved in this field?*
Joseph Frascella: I just found the brain is the most fascinating, complex structure in all of the universe. There's nothing more fascinating than studying the brain and its mechanisms, and the different processes that underlie behavior.

BW: *Is drug addiction a disease?*
JF: We like to think of it as a disease. Addiction is the result of a changed brain, and like many diseases, there is a change in the structure of the function and the end organ. The organ for addiction is the brain, and this change in brain structure and function changes behavior.

Drug abuse or drug use goes from a voluntary set of actions and behaviors—at some point something changes, and we're not quite sure about that something. We hear "a switch goes off," or you "spiral down"—at some point, voluntary behavior becomes involuntary. There is a change in the brain such that we are no longer able to control our behavior. That is one of the defining elements of addiction—where we no longer are in control of our behavior.

BW: *Why is it important to classify drug addiction as a disease?*
JF: It has to be treated as a disease, as something that has broken that needs to be fixed. We are trying to understand how the brain changes and how the changes relate to changes in our behavior. So given that you need treatment to "cure" the disease, the disease model makes a lot of sense. [It's better than] people thinking addiction as just a moral issue: bad people doing bad things. If you understand that addiction is a switch from voluntary to involuntary—once the choice is made, once you get into a compulsive drug-seeking state, when you're no longer in control—it's no longer a moral issue. It's a changed brain issue.

BW: *Does classifying addiction as a disease absolve people from responsibility of what was initially their choice?*
JF: People do make a choice to abuse drugs, but in a sense, it's a bit like Russian roulette. We don't know which people can dabble in substances—be it legal or illegal—and walk away, versus those who get addicted. We don't know enough about the brain and these individual differences that could put someone at greater risk to become addicted.

BEHAVIOR CAN CHANGE THE BRAIN TOO—AND THAT MAY BE THE WAY OUT FOR DRUG TREATMENT.

The recognition that this is a disease shows that the "just say no" attitude doesn't work. I *can't* stop any time I want—it's a changed brain, and it's very difficult. Most people need to go into treatment. This is a disease—a relapsing disease—and it's difficult to stop. People with diabetes need insulin all their lives. To put people in drug rehab for two weeks or 30 days and expect them to live a drug-free life—it's may be too much to ask for.

BW: *How do drugs affect the brain?*
JF: Drugs get into the brain and they affect certain receptors, transmitter systems. We've been looking a lot at the dopamine system. We know that all drugs of abuse function to release dopamine. Dopamine is also released when we have a good meal, hear a beautiful piece of music or see a piece of art that's appealing to us—these are natural rewards. But addictive drugs are so potent, releasing [so much] dopamine, sending signals to us that become very hard to resist—just as many people talk about certain foods that they find hard to resist because they taste so good.

BW: *Why are we built this way?*
JF: Our reward system has evolved over many thousands of years as a survival system. It's a

system that the brain has evolved—we repeat behaviors that are seemingly good for us, like feeding. If we didn't have a mechanism that told us we are hungry, we might forget to eat. Or for propagating the species. There are lots of things we do that are good for our survival, and we have this reward pathway that has evolved. So if we take in a meal that's high in calories, the brain says, "That's good! I should do it again!" Certain behaviors are very reinforcing.

BW: *Do all drugs affect the same parts of the brain?*
JF: No, but they all hit the central reward system and release dopamine.

BW: *What is the biological etiology of drug addiction?*
JF: We are really trying to study what are the individual differences—for some people it's genetic, for others it's environmental, or a mix of both. Certainly it's epigenetic [changes in the gene from the environment]. Why is it if I smoke a few cigarettes I might go on to have a long lifetime of nicotine addiction, whereas others can smoke lots of cigarettes but not become addicted?

It's a very complex bio-behavioral disease—it's not just neurological, because there's a lot of play between the brain and behavior. Our behavior can change our brain. We often think if we take a drug it will change our brain and our behavior changes, but it could be the opposite—and that may be the way out for treatment. We can engage in risky behavior if our phenotype is very impulsive and thrill-seeking, living fully and on the edge. That behavior could lead us to experiment with drugs. And behavior can change the brain, too. I think that will be some of our success in treatment: to change behavior then change the brain, not always looking to change the brain first.

BW: *What kind of behavioral treatments do you have?*
JF: We have a behavioral therapy where people are given behavioral strategies to deal with drugs and addiction, such as a set of studies on contingency management, where they are given reinforcers to come in with clean urine—food stamps, money, CDs. Even small reinforcers

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can change behavior and have people effectively abstain from taking drugs. A combination of medications and these treatments will be extremely effective treating the complexities of this disease we call addiction.

BW: *Is there a gene for drug addiction? Are there people or groups that are more resistant to drugs, similarly to the way that Asians and Jews have been found to be genetically intolerant of alcohol?*
JF: Our research is now trying to figure out what genes are involved. There are going to be certain subtypes, a certain genetic makeup for substance intake. Certain people will have certain genetics, so our treatments could be modified to better target different people. People respond differently to different medications, for example, not everyone takes the same blood-pressure medication.

BW: *How does medication treat drug addiction?*
JF: One approach is to go in and block the brain receptors and transporters that are affected by drugs of abuse. The approach is trying figure out which transmitter systems are involved, and target the medication at those transmitters' systems. If we know that a longtime cocaine abuser's system decreases the receptors and the amount of dopamine released, treatment would be to affect the dopamine system. How can we build up the dopamine system? We go and look at different brain systems. Can we go out and repair the systems that have been affected by chronic use and addiction?

The other strategy is to find genetic markers to determine if an individual is going to be responsive to this treatment or not. We can use brain imaging to see which individuals respond to treatment and which [do] not. We use fMRI and PET [Positron Emission Tomography] studies to measure what systems are effective. NIDA Director Dr. Nora Volkow uses PET imaging to look at the receptor systems, how they are affected by drugs of abuse.

We have a pretty good sense of how drugs of abuse affect the system. [But what we don't know is] does the brain normalize when they stop? Can we get it back to where it was beforehand? Do these brain changes affect the behavior?

BW: *How?*
JF: We know that drugs of abuse can affect cognitive processes, learning and memory. We see the brains of drug-addicted people have receptor deficiencies. But how about when you're in treatment—do these systems come back online, do you see a functional change? It's always important to see the structural changes—how these changes in the brain correlate with changes in behavior. Brain imaging gives us insight into how the brain changes are affected by drugs and might be affected by treatment. And in addition to uncovering generic markers, brain imaging is uncovering neurobiological markers. If we could look at someone's prefrontal cortex on a behavioral task and measure brain responses of drug-addicted individuals versus a control group, can we make some predictions correlated with brain changes? Can we predict how people will do in treatment?

BW: *What about prescription drugs? Do you deal with prescription drugs, too?*
JF: They work on the brain the same way, and cause addiction the same way. There are plenty of medications, like morphine, which has been a tremendously effective analgesic, but in the hands of someone abusing it you do run the risk of addiction. That should play into a doctor's prescribing. We are researching the effects of prescription drugs and looking at the same kind of questions we look at [with] other drugs. It's not off the table—just like we study addiction to nicotine, which is legal.

BW: *You are researching the impact of drug abuse and pregnancy. What have you found?*
JF: Generically, one can say that taking any foreign substance during pregnancy is not a good thing. We are studying drug exposure during pregnancy to try to find the effect on the developing fetus and the child. There are subtle changes—we have shown that there are some changes in birth weight, birth size, etc., and attention, learning and memory. Sometimes they are subtle and they may go away. As the kids get older we are trying to figure out if these are "life sentences," which hopefully they are not, given the right environment and right nutrition, etc. Maybe these effects might be minimal, and that is a good thing!

Another question that's important: If you have been exposed early on, does that put you at risk for becoming more vulnerable to drugs later? Are you more likely as a teenager?

BW: *You are also looking at drug abuse and the teenage brain. When is drug abuse most harmful? Is there an age where it's less harmful?*
JF: The earlier one starts with drugs, the more likely you are to become addicted. Vulnerability increases at age 12,13, 14 to be using drugs, and they are much more vulnerable to addiction. If we could keep kids from starting drugs at age 25 or older, we would find less problems with addiction. Not to say that if I start at 45 or 50 I would be totally protected, but statistics show that the earlier you start, the more likely it is you will become addicted.

I think there are critical times in brain development where drugs may have more influence than others. We also know the young brain tends to be a system in the "go" state, a state characterized by reward. The frontal areas develop last. These do the more executive function—the inhibitory control mechanism. A teenager might not think, "I could get in trouble, I might not get into the college of my choice," as opposed to the "go" saying, "To heck with my future, I am in the moment right now, and I want to do it." We know the adolescent's brain doesn't have the inhibitory systems. We know that the drugs of abuse affect those brake pads. The frontal regions are highly involved, and if drugs of abuse weaken those systems, and if you have weaker systems to start out, you could be in trouble as a teenager. That's why we are working really hard to come up with effective prevention strategies so that kids don't start taking drugs and run that risk of becoming lifelong drug abusers

BW: *How can parents prevent drug addiction?*
JF: Parents should try their best to educate their kids early on [about] drugs and unprotected behavior. Monitor them and be aware there will be instances where they will be tempted.

BW: *What about children and prescription drugs?*
JF: We have to keep in mind that there are these things we call drugs and clump them into one category. Medications are very effective at treating whatever the medical issue is when prescribed properly and adhered to properly, [as opposed to] if you take a medication for non-medical purposes. We can't lump everything together and say all medications are drugs and drugs are bad. I've seen firsthand where kids very near and dear to me needed drug medications and wouldn't function without them. **[bw]**