

## Reflections on the Past 40 Years of Drug Abuse Pharmacology Research

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The major theme I see as having developed over the past 40 years in our pharmacological approach to addictions is the application – and the demonstrated applicability – of the principles of behavioral psychology to the study of drugs and of drug effects. The two specific core behavioral pharmacological principles that I see as having had the greatest impact on the drug abuse field are: (1) that some drugs can function as behavioral reinforcers that can develop and sustain the behavior of self-administration; this is the notion of the biological normality and universality (or near-universality) of vulnerability to drug reinforcement and drug abuse; and (2) that drug action and drug reinforcement result not just from pharmacology, but from context and environmental alternatives, and from learning and the past history of the individual; this is the notion of drug taking and substance abuse being learned behavioral disorders.

Previously, the individual differences in addictive behavior evident in the general population– i.e., that some people became abusers or addicts, and some did not – were attributed to moral or characterological flaws in substance abusers, or perhaps to genetically inherited flaws related to vulnerability or self control. Whatever the basis, substance abuse and addiction were seen as problems of a flawed minority.

The development of animal drug self-administration models is probably the single greatest scientific advance that has freed us from this earlier view of substance abuse risk and vulnerability being relevant only to a flawed minority of the population. The development of these animal laboratory models was an incredibly important scientific advance. It highlighted the biological normality of drug reinforcement and the universality, or near-universality, of vulnerability to drug reinforcement and drug abuse.

These factors, in turn, emphasized the critical role of environmental factors, experience, and learning as determinants of which individuals did or did not come under the sway of drug reinforcement. A great practical advantage of this realization and this behavioral/learning conceptualization was that the science was directing causal, mechanistic attention to a domain of factors that are not only explanatory but that are also amenable to influence and intervention.

We now have decades of research documenting the applicability of behavioral learning principles and processes to addictive disorders. It is now clear that drug actions are powerfully influenced by both classical (Pavlovian) learning processes and operant (Skinnerian) learning processes. Tolerance, previously thought to be a purely pharmacological process, is now known to be in part a learning process. Whether a drug will function as a reinforcer to sustain self-administration behavior is now known to be influenced by the conditions and contingencies and learning experiences related to drug

availability, and also to those related to the availability of alternative behavioral options as well.

It has been impressive to see the extent to which animal laboratory models of addictive processes have repeatedly been validated by the documentation of similar relationships both in animals and in human drug abusers. This cross-species validation and generalization of principles between the laboratory and the clinic has been a great strength of the behavioral pharmacological view of addiction.

The success of the behavioral pharmacological view of addiction in offering both explanation and effective interventions has contributed to its extension to a broad variety of self-administered substances. Extensive cross-drug commonalities have been noted in the relationships of pharmacological and environmental/behavioral factors to drug self-administration. Also, varieties of substance self-administration not previously considered as “addictions” – e.g., tobacco, caffeine – have now come to be seen and understood in this same framework.

The field of drug abuse liability assessment is one that has seen extensive development over the past four decades. Behavioral pharmacological methods such as drug self-administration and drug discrimination lie at its core. Conceptually similar methods are used in animals and humans, and there is substantial cross-drug commonality in assessment methods. The methods have grown considerably more sophisticated over the years – moving from methods that gave largely categorical answers (“Is this drug self-administered?”), to using more fine-grained choice and progressive ratio and behavioral economic assessments that can better evaluate and rank order drugs in terms of their reinforcing effectiveness and robustness and overall abuse liability.

These abuse liability assessment methods have also been productively adapted for application to the task of medications development assessments – testing potential pharmacotherapies to determine whether they reduce the effects, self-administration, and apparent abuse liability of their targeted drug of abuse. These methods, in both animal laboratory and human laboratory, have the potential to provide very cost effective guidance regarding which potential pharmacotherapies appear most promising and most deserving of further evaluation in large scale clinical trials.

Methadone, buprenorphine and naltrexone are the great drug addiction pharmacotherapy development success stories of the past decades. Methadone achieved its adoption and success through the bold clinical innovation of Dole and Nyswander, without extensive prior development laboratory research for the addiction indication. Buprenorphine and naltrexone, on the other hand, have both been developed step-wise through the more orderly process of sequential animal and human laboratory studies followed by subsequent clinical trials. All three are pharmacological wonder drugs, with great efficacy in interrupting addictive processes. But none has yet been fully embraced into adequate clinical practice delivery to patients. Methadone continues to struggle for public, community acceptance. Naltrexone continues to struggle for adequate acceptance and use by patients. Buprenorphine is the newcomer to the addiction treatment

marketplace. Its degree of success and acceptance may be critically determinative of the willingness of pharmaceutical companies to invest in development of addiction treatments. Buprenorphine is an especially interesting case, since its primary marketed dosage form (the buprenorphine-naloxone combination) is an engineered dosage form specifically designed to incorporate the behavioral principles of reinforcement and punishment so as to encourage appropriate use and discourage inappropriate use. If the medication is taken as directed (sublingually) only the reinforcing buprenorphine achieves significant biodelivery. However, if taken inappropriately by injection the antagonist naloxone portion is fully delivered and can precipitate an aversive withdrawal reaction in dependent individuals.

The value of the behavioral pharmacological perspective to the substance abuse field is reflected in part by the growth of behavioral pharmacology research; but it is reflected also in the broad embrace and use of behavioral pharmacological methods by other disciplinary approaches to studying substance abuse and addiction. For example, it is impressive to see the extent to which such methods as drug discrimination and drug self-administration have been adopted and become widely used as tools in neurobiology and neuroscience research on addiction.

Behavioral pharmacological understanding of drug abuse and addiction has also had a significant impact on clinical therapeutics and clinical trials. For all varieties of addictive disorders the most common treatment is counseling based on cognitive behavioral procedures that emphasize the risks posed by drug-related environmental stimulus conditions, that emphasize the importance of developing rewarding, non-drug-related competing behavioral alternatives, and that emphasize the importance of motivational or incentive-based approaches for discouraging drug use and for encouraging competing alternative behaviors. This type of behavioral or cognitive-behavioral treatment is now widely accepted as the appropriate psychosocial treatment platform upon which to conduct clinical trials of potential pharmacotherapies for addictive disorders.

The importance and contributions of the behavioral pharmacological perspective and behavioral pharmacological science are reflected in our national history with tobacco over the past few decades. The Surgeon General's report on Tobacco Addiction, and then the more recent revelations that the tobacco industry was well aware of tobacco's addictive characteristics and explicitly designed their products and their marketing campaigns so as to promote addiction while publicly denying that addiction was relevant to tobacco use, were transformative events for our national tobacco policy. This policy transformation was built on a foundation of behavioral pharmacological research on tobacco and tobacco dependence.

I see several areas as special challenges and opportunities for the future research attention and development.

One is the role of genetics in addiction. Behavioral psychology and behavioral pharmacology have tended to ignore or minimize the roles of individual differences and

of genetics. In general, the behavioral view of addiction has been far onto the “nurture” end of the nature-nurture continuum – taking the view that addiction vulnerability is universal (or nearly so), and that the major determinants of addictive behavior lie in environmental conditions and contingencies and in experiential learning. However, extensive data – both animal and human – make clear that genetics play an important role in addiction vulnerability and risk. We are just at the early stages of learning the nature of this role, and the full story is likely to be quite complex. It appears there are some genetic risk factors that are drug-specific (i.e., opioid vs. alcohol vs. tobacco dependence), and some that are non-specific (perhaps more like a personality-related vulnerability factor), and it also appears there may be separate genetic risk factors related to the initiation of substance use experimentation versus the progression from use to abuse and dependence. We also know (or believe) that many individuals initiate use and progress to addiction without any as-yet-identified special risk factors (i.e., supporting the universal vulnerability notion). The challenge for the future is to learn much more about all this genetic diversity and, most importantly, to learn how it can be made relevant and useful to the tasks of preventing and treating substance abuse. We have yet to see whether the specific nature of individuals’ genetic vulnerability profile can be used to guide pharmacotherapy development and/or pharmacotherapy selection, and whether different pharmacotherapies might be specific to or have differential effectiveness in different types of individuals. The continuing exploration of genetic risk factors will be most useful, of course, if it is able to move beyond the stage of identifying increased risk and enter the stage of guiding therapy development and individualized therapy selection.

A second area of challenge and opportunity for future research is the question of the extent of pharmacological specificity of various procedures, mechanisms and interventions across different varieties of substance abuse. From the pharmacological perspective we tend to think of different varieties of substance abuse as being very distinct and as involving quite different neuropharmacological mechanisms, and we tend to expect that pharmacotherapies will likely have a fairly narrow pharmacological specificity for a particular types of substance abuse (e.g., opioid vs. CNS stimulant vs. sedative/hypnotic vs. alcohol). However, to the extent that different varieties of substance abuse may involve common, non-specific vulnerability factors, or may involve common neurocognitive or affective elements, or may share final common pathways, then we may discover non-specific pharmacological treatments that have efficacy across pharmacologically different varieties of substance abuse. Learning more about the specific mechanisms involved in substance abuse development (i.e., pharmacologically specific mechanisms versus non-specific mechanisms) may have a great impact in directing our search for effective pharmacotherapies.