

Addiction Treatment in the Era of Translational Medicine

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Abstract

A number of recent advances have added to our understanding of addiction as a complex brain disease. These include: 1) the identification of the human genome and rapid technological advances in the field of genomics; 2) the establishment of related fields of inquiry in molecular biology including proteomics, metabolomics, and epigenetics; 3) the evolution of genome-wide association studies; 4) the increasing sophistication of neuroimaging techniques making visible at ever smaller resolution functioning in specific brain regions; 5) continued investigation into brain neuroplasticity and how this contributes to and is shaped by pathophysiologic states; 6) an emphasis on the identification and application of best-evidence and best-practices in the clinical practice of addiction medicine; and, 7) an expanding armamentarium of useful already established pharmacologic agents which have anti-addiction properties and the promise of new agents based on specific causation. These technological and scientific advances coupled with informed clinical inquiry offer the promise of more direct and expeditious bidirectional communication between the research and clinical communities, a process that has come to be known as *translational medicine*. The application of these principles to individual clinical care offers the promise of care based on an individual's particular biology rather than disease state; this field of endeavor has come to be labeled *personalized medicine*.

Within the field of addiction psychiatry, both translational and personalized medicine offer the promise of more steady progress where substantive change has occurred incrementally over the past three and one-half decades. Despite the progress and promise, there exists a need to proceed judiciously, and barriers to change need to be understood and addressed in the historical context in which addiction treatment has developed in the United States. The paper will address this history, key definitions, forces likely to advance the practice of addiction medicine in the next decade, potential barriers to change, and the changing dynamics of the physician-patient relationship in treatment and recovery.

Background: A Brief History of Treatment and More Recent Challenges

Modern approaches to the treatment of alcoholism in the United States can be traced to the pioneering work of Drs. William Silkworth and Edward Jellinek, as well as the networking which occurred in the context of the so-called "Oxford Groups" so-named by a group of Oxford alumni who had aligned themselves with the philosophy of Frank Buchman. The indirect

association of the founders of Alcoholics Anonymous with these groups played a role in the establishment of AA in 1935. (Kurtz 1979) A keystone of AA was the understanding of alcoholism as an illness amenable to interventions free of moral judgment.

While medical interventions were limited at that time to detoxification efforts and the support of other alcoholic individuals in recovery, by mid-century a hybrid model of treatment emerged, known as the Minnesota Model. This utilized the disease concept of alcoholism re-introduced popularly by Jellinek, and the twelve-step approach of AA in a standardized, “one size fits all” manner. (Cook 1988) What developed from this approach was a standardized, 28 day inpatient approach to the treatment of alcoholism based on the disease concept, with programmed lectures, active engagement in group therapy, and AA attendance that came to dominate non-opioid addiction treatment paradigms for the next thirty-five years.

Economic forces in the mid-1980’s, occasioned by upward inflationary pressure in the healthcare arena, the lack of evidence that more expensive inpatient care was any more effective overall than less expensive outpatient care, and the establishment of the managed care industry began to forcefully challenge this model. In addition, with the introduction of the concept of *dependence* by Edwards and Gross, a gradual shift began, focusing on earlier intervention efforts involving the broad spectrum of alcohol problems rather than solely on more advanced cases of alcohol addiction. (Edwards 1976) An additional shift occurred de-emphasizing treatment setting and emphasizing the intensity of intervention. Specific manually driven and reproducible psychosocial interventions such as cognitive-behavioral therapy, family therapies, motivational enhancement and more specialized group therapy techniques were introduced and added to the development of a very different treatment paradigm. In time patient placement criteria, with the preeminent model being that developed by the American Society of Addiction Medicine, added an important degree of objectivity that contributes to more systematized treatment and treatment outcomes research. (ASAM 1996)

While the hard science of the pathophysiology of alcohol and other non-opioid addictions strayed far behind the economic forces shaping change, the same cannot be said for the development of more specific interventions for the care of those addicted to opioids. An *abstinence only* model for most opioid addicts was associated with a miserably high rate of recidivism outside of intensely monitored programs such as therapeutic communities, and remained so until the introduction of methadone maintenance by Dole, Nyswander, and Kreek in 1964. (Dole 1965) Opioid agonist therapies, when properly applied and administered, have been associated with substantial cessation of rates of illicit use, an improved quality of life for compliant individuals, sharp drops in crime directly and indirectly associated with illicit opioid procurement, and normalization of trait physiologic parameters associated with the actively addicted state. (Kreek 2005) Access to treatment however, has been limited by a number of statutory and social factors, until the introduction of buprenorphine maintenance (offered in the general medical setting by specially trained providers) earlier in this decade judiciously circumventing many of the statutory barriers which previously existed for methadone maintenance programs. (O’Brien 2004) Despite its success, the maintenance strategy has been the focus of at times intense criticism. Despite the criticism, the story of translational medicine as applied to the study of addictive disease may indeed have its earliest roots in the ongoing

research done on opioid physiology at Rockefeller University and other institutions since that time. (Kreek 2005)

As science has lagged behind treatment driven more by ideology than pathophysiology, it is reasonable to ask what can be reasonably concluded from the research literature thus far. This may be summarized as follows: 1) until recently, most research has proceeded utilizing a restricted concept of treatment, with exclusionary study selection criteria producing study populations bearing less than ideal resemblance to real world patients; 2) treatment interventions result in better outcomes than no treatment; 3) longer retention times in treatment result in better outcomes; 4) no one form of treatment is superior to others for unselected groups of alcoholics; and, 5) different types of treatment seem to have different rates of effectiveness when examined using individual patient variables.

“Success”, a term used ubiquitously within the treatment field, remains elusive for many despite the incremental advances that have occurred during the last three decades.

A number of recent advances have added to our understanding of addiction as a complex brain disease. These include: 1) the identification of the human genome and rapid technological advances in the field of genomics; 2) the establishment of related fields of inquiry in molecular biology including proteomics, metabolomics, and epigenetics; 3) the evolution of candidate-gene and genome-wide association studies; 4) the increasing sophistication of neuroimaging techniques making visible at ever smaller resolution functioning in specific brain regions; 5) continued investigation into brain neuroplasticity and how this contributes to and is shaped by pathophysiologic states; 6) an emphasis on the identification and application of best-evidence and best-practices in the clinical practice of addiction medicine; and, 7) an expanding armamentarium of useful already established pharmacologic agents which have anti-addiction properties and the promise of new agents based on specific causation. These technological and scientific advances coupled with informed clinical inquiry offer the promise of more direct and expeditious bidirectional communication between the research and clinical communities, a process that has come to be known as *translational medicine*. The application of these principles to individual clinical care offers the promise of care based on an individual’s particular biology rather than diagnosis alone; this field of endeavor has come to be labeled personalized medicine.

Within the field of addiction psychiatry, both translational and personalized medicine offer the promise of more steady progress where substantive change has occurred incrementally over the past three and one-half decades. Despite the progress and promise, there exists a need to proceed judiciously, and barriers to change need to be understood and addressed.

Definitions

Fundamental to any meaningful discourse is clarifying key terms that shape that discussion. For our purposes, these terms include: 1) *addiction*; 2) *treatment*; 3) *success*; 4) *recovery*; 5) *translational medicine*; 6) *personalized medicine*; and, 7) *implementation research*.

The term *addiction* has many definitions, and selection of an appropriate term currently rests on contextual and linguistic considerations. While a number of definitions were surveyed, the authors note that the definition as proffered by the American Society of Addiction Medicine

contains those key concepts reliably associated with the addiction syndrome. (ASAM 2001) Herein addiction is defined as a primary, chronic neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over use, compulsive use, continued use despite harm, and craving.

In 1991, the Institute of Medicine published a landmark work entitled “Broadening the Base of Treatment for Alcohol Problems” that provided an exhaustive analysis of the extant treatment literature to that time; it also endorsed extant efforts at earlier intervention and expanded the concept of treatment by attempting to dispel the notion that problems that fell short of dependence were necessarily less severe than dependence itself (a notion that is now supported by empirical evidence). (Institute of Medicine, 1990) Therein the IOM put forth the Committee recommendation that *treatment* be defined as “the broad range of services, including identification, brief intervention, assessment, diagnosis, counseling, medical services, psychiatric services, psychological services, social services and follow-up, for persons with alcohol problems”. They went on to define the overall goal of treatment to be “the reduction or elimination of the use of alcohol as a contributing factor to physical, psychological, and social dysfunction, and to arrest, retard, or reverse the progress of any associated problems.”

Against this backdrop, the term *success* has been an elusive one indeed and continues to defy easy characterization or definition. While the term has been used repeatedly within the treatment literature with various connotations and motivations in use, the limited understanding of the term ultimately lies in two broad domains: 1) the limitations in our knowledge of the pathophysiology linking genetic expression to behavior and the lack of animal models that parallel the complex experiences of human beings, and, 2) the cross-sectional nature of the term implying a process that contradicts the known natural history of alcoholism and other addictions. Perhaps because of these limitations, the term *recovery* has become of greater interest in the field as it relates more meaningfully to the natural history of alcoholism and other addictive disorders. Recently, a consensus panel from the Betty Ford Institute has offered an operational definition of recovery, incorporating both abstinence and quality of life in the context of lifelong relapse prevention efforts. *Recovery* according to this group is a voluntarily maintained lifestyle composed of and characterized by sobriety, personal health, and citizenship. Sobriety was further defined by length (early, less than one year; sustained, one to five years; and, stable, greater than five years). Personal health implies an improved quality of personal life as measured by the World Health Organization’s Quality of Life profiling instrument. Citizenship was defined by this group as living with regard and respect others as defined by the social and environmental scales of the WHO-QOL. (Betty Ford Institute Consensus Panel, 2007)

The term *translational medicine* refers to that branch of medical research that attempts to more directly connect research in the basic sciences to patient care. (Mankoff 2004) *Personalized medicine* refers to the clinical use of information from a patient’s genotype, level of gene expression, and/or other clinical information to stratify disease, select and provide a therapy, or initiate a preventive measure particularly suited to that patient at the time of administration. (Piquette-Miller 2007) *Implementation research* reflects upon the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and hence to improve the quality and effectiveness of health services and care.

(Madon 2007) The importance of this and its impact on global health has recently been reviewed. (Waldman 2007)

With these definitions in mind, the central question in treatment is unchanged from that noted in the Institute of Medicine study previously referenced, namely “ Which kinds of individuals, with what kinds of alcohol or other addiction problems, are likely to respond to what kinds of treatments by achieving what kinds of goals when delivered by which kinds of practitioners?” (Institute of Medicine 1990) Prior treatment efforts have tended to focus on variably defined outcomes averaged across large groups of alcoholics. As the complexity of alcoholism, for example, has been delineated as multidimensional in character, this bygone notion of uniformity and the one-dimensional nature of treatment associated with it has become anachronistic and is *beginning* to yield in practice newer and more complex treatment paradigms that at least attempt to meet the needs of individual patients. (Moss 2007) Our nosology, which has emphasized reliability over validity, has not kept pace with evolving scientific research whose progress continues at an increasing pace. (Hyman 2007)

Translational and Individualized Medicine: Forces of Change

Multiple forces, both within the context of medicine and its associated disciplines, as well as social forces in the realms of politics, economics, and cultural expectations offer promise to effect change in the manner in which medicine is practiced in the future as well as in the mechanisms in which scientific inquiry influences public policy. Multiple presentations elsewhere in this volume underscore the need in the United States as well as in the global community for a more rational, timely, and scientifically informed public policy as it relates to the addictive disorders. For example, an emphasis on interdiction alone is woefully inadequate as dramatically underscored by the fact that at the Port of Los Angeles alone, only 400 of 130,000 cargo containers that arrive monthly are subject to search. Just one container contains the amount of heroin it would take to satisfy the “needs” of the United States for one year for the illicit substance. (David Redford, New Mexico State University, personal communication) Jails and prisons are woefully overcrowded due to the surge in drug use convictions without any attention to treatment or subsequent secondary or tertiary prevention efforts. Indeed, the concept of *primary prevention* offers a prime example of how priorities in the public sphere may be valuably shaped by scientific research.

Recent research has suggested that the onset of alcohol dependence peaks at age 18, and rapidly declines after the age of 25. (Li 2004) While the impact of alcohol, and to a lesser extent other substances, has been researched in the fetal brain, the extent to which an addictive substance negatively impacts the developing central nervous system is less well known. Recent reviews have focused on the impact of substance exposure to an immature brain and the challenges involved in interpreting these studies. (Clark 2008) What is known is: 1) those areas of the brain that are the last to mature neurologically in normal development are also those that are involved in sustaining addiction in the adult; and, 2) the longer the frequent use of an addictive substance can be forestalled, the less likely one is to become addicted. This has far-reaching effects at all levels.

It is the ultimate goal of personalized medicine to identify individuals who are at-risk for any pathophysiologic process and to prevent the onset of symptoms of that process. As this information base is not known for most illnesses, the goal then defaults to the arrest, retardation, or reversal of pathological changes that underlie specific symptoms. With the successful sequencing of the human genome and documentation of patterns of genome-wide variation and linkage disequilibrium in several population studies (e.g HapMap project) the ability to quickly move beyond previous genetic efforts involving twin, adoption, and linkage studies becomes possible. Within the past three years, genome-wide association studies in which high-throughput genotyping technologies seek to identify statistical association of single-nucleotide polymorphisms with clinical conditions and measurable traits have supplemented and in some cases eclipsed association studies as the most efficient means of identifying potential genes or sets of genes that may be associated with either vulnerability or resistance to disease, or that may be involved in the causation of a particular condition. (Pearson 2008) Recent advances in epigenetics have yielded insights into how particular exogenous circumstances can influence imprinted genes, turning them on and off, and in some cases playing a key role in disease production. (Feinberg 2008). While this has been most clearly studied in cancers and conditions associated with aging, a recent report has noted an association with chromatin change and alcohol dependence under conditions of stress. Thus, understanding how genes interact with each other, and how genetic expression is influenced by environmental stress in its nascent stages, it does offer the promise of a greater understanding of how genetic expression influences behavioral change through the intermediate stages of translation, neurochemical change, alterations in neural connectivity and synaptogenesis and higher levels of neurobiological integration.

Complementing genomic studies have been the advances in both structural and functional neuroimaging techniques that pursue ever greater degrees of visual precision in combination with genomic and biochemical analysis to capture a snapshot of what may be going awry in disease states when compared with normal function. These combined investigative approaches have led to recent conceptualizations of some disorders, such as bipolar illnesses, as disorders of neuroplasticity implicating genetically influenced disorders of synapses and circuitry with faulty informational processing along nerve cell signaling pathways. Both structural and functional neuroimaging techniques play a critical role in such assimilative research efforts. Indeed recent research has conceptualized “disorders of neuroplasticity” implicating genetically influenced disorders of synapses and circuitry. The recently established field of metabolomics seeks to identify disease states based on aggregates of biochemical molecules that leave a characteristic “signature”, in association with particular disease states. (Daouk 2008)

From a clinical vantage point, the expanding array of “top down” established therapeutic agents (i.e., those agents approved for other uses with discovered benefit in treating addiction - naltrexone, acamprosate, disulfiram, topiramate, and baclofen) makes it incumbent on the clinician to be more familiar with the neurobiology of addiction in order to rationally prescribe these agents. (Heilig 2006) Similarly, pharmaceuticals derived from the so-called “bottom-up” approach are developed specifically in response to a hypothesized specific causation (eg. current neurokinin 1 receptor antagonists) offer promise for more specific and possibly more effective and long-lasting treatment efficacy. (George 2008) As pharmacotherapy expands, capacity to access treatment services in non-traditional settings will likely expand as well.

Barriers to Bridging the Gap between Research and Practice

Carving nature at its joints both in the research and clinical settings is an iterative process fraught with challenges without guarantees of success and thus is not an undertaking for the fainthearted. A number of barriers exist at the interface between research and practice that may impede bidirectional discovery and communication. These include lack of information among caregivers and exposure to the illness and the potential for recovery, difficulties inherent in changing attitudes about illnesses where stigma prevails both among caregivers and among patients at the point of care, tradition driven by dogma, and limitations imposed by technological restrictions or lingering systems of classification based not on causation but on phenomenology. From a public policy perspective, the lack of access to quality scientific information and the dearth of communication between disciplines that normally would not talk to one another as a matter of routine, directly impacts on economic realities that researchers and clinicians must face. Finally, the communications divide between researchers and clinicians is influenced by pragmatic, economic, ideological, informational and training parameters. (Stettler 2008)

In order to effectively treat any condition, one must be able to muster enough of an index of suspicion to investigate its possibility. A major challenge that clinicians face in this arena is the lack of effective training at all levels of clinical practice. Alcohol dependence remains substantially underdiagnosed, even in psychiatric settings. (Woodward 1991) Patients are often quite reluctant to discuss with their caregivers a problem loaded with social stigma and personal shame. As a result, patients suffering from addiction are often perceived as misanthropic, mendacious, time consuming and defensive. Physicians may overlook conditions for which they feel they will have little impact on. The attitude displayed by the caregiver in such a situation is critical to conducting appropriate diagnostic screening and optimizing patient cooperation and truthfulness. Information alone is not a sufficient condition to overcome the sense of therapeutic nihilism fostered by social stigma and the lack of role models in training. Improvement in diagnostic acumen must be accompanied by attitudinal change, usually effected by exposure to individuals who have and continue to make a successful recovery effort.

Another barrier exists in the limitations that our current classification systems place upon us. While current psychiatric nosology based upon phenomenologic observation have successfully stressed greater reliability in diagnosis across systems and cultures, the evolution of genomic and related sciences as well as neuroimaging have now provided tools to explore pathophysiologic mechanisms which may not respect these phenomenologic boundaries, and highlights the need for greater biologic validity in future studies. Clinical examples highlighting this include the concept that the psychopharmacologic drugs we administer may choose the disease rather than the traditional concept of the disease choosing the drug. Diagnostic validity remains a frontier of great promise and indeed one in which effective treatment of the future resides.

The nosologic challenges in the near future emphasize the role of neuroscience to reliably define the boundaries of valid diagnostic entities based on specific responses to specific therapeutic interventions. This process is an iterative one that will necessarily rely upon a dynamic system of nosologic classification that allows the flexibility to update itself in an expeditious fashion, and in particular between the decade-plus long interludes between classification system updates.

Hyman, in a recent review, suggests the need for “shadow” research criteria in the DSM-V that expand upon the concept introduced in the DSM-IV, and suggests that three specific alternatives alone, or more effectively in combination, may facilitate this process of self-critique and expediting nosologic change. (Hyman 2007) These include: 1) considering measures of dimensionality in specific disorders and their presentations; 2) symptom cluster assessment; and, 3) an emphasis on spectrum disorders. It is worth pausing to consider each of these options.

With regard to dimensionality, it is reasonable to assume that most disorders in medicine, can be considered in a dimensional context. While at a syndromic level this is apparent for many disorders, such as hypertension, diabetes, and coronary artery disease, other disorders may present with subsyndromal manifestations which while not classifiable as “disease” may nonetheless be harbingers of problems to come or may be associated with a degree of dysfunction. Clearly, from a pathophysiological and phenomenological perspective, psychiatric disorders can easily be viewed from a dimensional perspective in disease progression, severity, and the degree of dysfunction suffered. An artificially determined dichotomous vantage point leads to limitations in phenotypic understanding between disease states that seem to share close associations, such as depression and anxiety, and ultimately constriction in the investigation of causation and identification of effective therapies.

Symptom cluster analysis implies an unpacking of currently defined DSM-IV diagnostic categories into clearly conceptualized pharmacological and dysfunctional clusters. Hyman offers the example of positive, negative and cognitive symptoms that characterize the schizophrenic disorders. Recent research has demonstrated that there are more likely to be manifestations of common neurologic and by extension genetic, proteomic and/or metabolic changes underlying such considerations which minimize the limitations placed by arbitrary classification and emphasizes relationships based on real- time brain system dysfunction.

Alternatively, a spectrum-based approach may be defined as a group of disorders related through risk genes “lumped together”, at the risk of adding to heterogeneity of the study populations. The advantage of this approach is that it encourages an inductive “bottom-up” re-analysis of phenotypes, examining familial aggregation of symptom clusters and the segregation of symptoms across generations. For example, it could be asked how measures of grey matter thinning correlate with quantitative measures of cognitive change in schizophrenics, with symptoms, structural findings, and functional neuroimaging correlations made with genetic risk factors as they emerge.

Finally, a substantial communications divide exists between researchers and clinicians, and even within the various disciplines that represent clinical caregivers. These are influenced by pragmatic, economic, ideological, informational and training parameters and have recently been reviewed by McGovern in a discussion on the research to practice gap. (McGovern 2004) He emphasizes the importance of interdisciplinary communication between all stakeholders including clinicians, administrators, regulatory agencies, and researchers. To this list we would add the input of patients themselves. Pragmatically, such an “innovation-to-organizational” fit must be implemented in terms of individual culture. Mittman (Mark Willenbring, personal communication, December, 2008) has likened the impact of these dynamic forces upon treatment as pliable bands (representing semantics, advocacy, intellectual, regulatory, economic,

ideological, tradition, training, and social forces) attaching to and suspending a concrete block representing treatment itself. Ultimately a transformation in the substance of treatment from a more rigid entity to that of a more flexible, gel-like capsule represents a more dynamically poised system ready to change with the times as may be appropriate.

While national technology transfer studies including Project MATCH, the NIDA Clinical Trials Network and “Blending Conferences” and CSAT’s Cannabis Youth Project have sought to bridge the research to practice gap at a macro level, McGovern has examined clinicians and administrators attitudes towards innovations in treatment. (McGovern 2004) Curiously, among most addiction care providers, there appears to be continued resistance to the use of medications specifically targeting addiction as the least amenable to change among all parameters studies. Clinicians as well as patients are subject to the vicissitudes of the process of change as outlined by Prochaska and DiClemente.(Prochaska 1986) There exists a need for clinical scholars who can reach out to bridge these gaps with their colleagues as well as with other disciplines in the medical sciences. Basic scientists need to be rewarded for clinical communications initiatives, and clinicians otherwise overwhelmed with day to day clinical demands need to be provided with quality data of importance to clinical practice in order to effect change. Finally, the use of evidence-based guidelines, the identification of appropriate metrics of outcome, and the delineation of performance gaps with feedback loops with mechanisms to effect change with further reassessment need to be part of every treatment program.

Hypothesis driven research alone cannot meet the needs of translational medicine as experimental models are not always translatable into human pathology. Reality based research hypotheses are based on the concept that direct human observation may legitimately lead to testable hypotheses. Kreek et al have reviewed such an approach within a bidirectional translational hierarchy at their institution that has informed over four decades of research at their facility. (Kreek 2005) Critical to this process is the effective gathering of high quality reliable clinical data in which outcomes are tracked.

The Physician-Patient Relationship

Ultimately, the most important impact of the introduction of new technology to the practice of medicine, and in this case psychiatry, rests in the effect that it has on the physician-patient relationship. Traditionally this relationship has taken on the trappings of a form of Cartesian reductionism that views the body as a machine and the physician as a technician whose job it is to repair that machine. However, in recent years this dichotomous way of thinking is giving way to a more complex and fulfilling notion: that the doctor-patient relationship is in its essence one of healing. In the philosophical model of medicine advanced by Pellegrino and Thomasma the center of medicine is relationship, with the central purpose of the relationship healing. (Pellegrino 1981) Technical competence, including incorporation of appropriate new technologies, is not denied in this model. As both authors point out, “the act of medical profession is inauthentic and a lie unless it fulfills the expectation of technical competence...however...Competence must itself be shaped by the end of a medical act, a right and good healing action for the patient.” (Ibid)

Scott et al have built upon this foundation to describe the Healing Relationship Model. (Scott 2009) In this model, healing is defined as “being cured when possible, reducing suffering when

cure is not possible, and finding meaning beyond the illness experience.” Critical to this relationship are mutual respect (valuing), a recognition of the inherent asymmetry of the relationship (appreciating power), and continuity (abiding). On the part of the patient three outcomes are critical, including trust (a willingness to be vulnerable), hope (that some future beyond the present suffering is possible), and a sense of being known. (Parenthetically, the word *patient* is etymologically traced to the Latin verb *patior*, to suffer.) On the clinician’s side of this relational equation are four essential clinical competencies: self-confidence, emotional self-management, mindfulness, and clinical knowledge. (Ibid.) Of particular import to our discussion of pharmacogenomic testing is what this latter competency implies: the store of knowledge of empirical medicine, and *the ability to synthesize and tailor that knowledge for the benefit of a particular individual*. These factors influence the bidirectional accuracy and flow of information between physician and patient, helping to insure a cooperative spirit with mutually agreed upon treatment goals and components. An example of this is receptivity to medication use and compliance. Other discussions of the physician-patient relationship, particularly in Western culture, have centered on the four pillars of ethical reasoning, including beneficence, autonomy, non-maleficence, and justice, as well as an analytic assessment of the asymmetric nature of the relationship and power of the physician as a fundamental consideration, as found in the work of Michel Foucault.

One could argue that properly applied, the forces of translational medicine and psychiatry have the potential to enrich the physician-patient relationship and move the practice of psychiatry beyond one of a reactivity to a hybrid of reactivity and proactivity, one that is consistent with the healing relationship model as noted above.

Summary

Alcoholism and other addictions represent a major public health threat worldwide; alcoholism alone has been identified as one of the ten leading causes of morbidity and mortality across the globe, accounting for nearly 4% of deaths annually. (World Health Organization 2002) As this is a potentially preventable illness, we can no longer afford the ten year gap of research to practice. The solution to this involves all stakeholders in treatment, including clinicians, administrators, regulatory agencies, legal and social policy makers, research prioritization and patients. In order to effect change reflecting scientific advances, we must address the pragmatic, economic, ideological, informational, and training barriers. It is important to identify best practices via evidence-based mental health sources, understand our own position in the stages of change cycle, and be open to self-criticism in order to expand our own epistemic capital.

This will require a major paradigm shift to include an emphasis on reality based clinical hypothesis generation blending with more traditional theoretic mechanisms of hypothesis generation and testing. Application of these principles will require an innovation to organizational fit. It will be necessary to consider collaborative efforts in treatment with all stakeholders, including researchers, clinicians and patients. It also implies the establishment and ongoing curation of a reliable and valid data infrastructure available to evolving technologies that will enrich the relationship between research and clinical practice.

References

- 1) American Society of Addiction Medicine, American Pain Society, and the American Academy of Pain Medicine: Definition of Addiction. 2001.
- 2) American Society of Addiction Medicine: Patient Placement Criteria for the Treatment of Substance-Related Disorders, Second Edition. American Society of Addiction Medicine, Chevy Chase, MD, 1996.
- 3) Betty Ford Institute Consensus Panel: What is recovery? A working definition from the Betty Ford Institute. *J Subst Abuse Treat* 33: 221-228, 2007.
- 4) Clark D, Taper S: Introduction to alcohol and adolescent brain development. *Alc Clin Exp Research* 32(3):373-375, 2008.
- 5) Cook CC: The Minnesota Model in the management of drug and alcohol dependency: miracle, method, or myth? Part I: the philosophy and the programme. *Br J Addict* 83:625-634, 1988.
- 6) Daouk R: Metabolomics: A global biochemical approach to drug response and disease. *Ann Rev Pharmacol Toxic* 48:23.1-23.31, 2008.
- 7) Dole VP, Nyswander M: A medical treatment for diacetylmorphine (heroin) addiction: a clinical trial with methadone hydrochloride. *JAMA* 193:80-84, 1965.
- 8) Edwards G, Gross M: Alcohol dependence. Provisional description of a clinical syndrome. *Brit Med J* 1, 1058-1056, 1976.
- 9) Feero WG, Guttmacher AE, Collins FS: The genome gets personal-almost. *Journal of the American Medical Association* 299(11): 1351-1352, 2008.
- 10) Feinberg A: Epigenetics at the epicenter of modern medicine. *JAMA* 299(11):1345-1350, 2008.
- 11) Feinberg AP: Epigenetics at the epicenter of modern medicine. *Journal of the American Medical Association* 299(11): 1345-1350, 2008.
- 12) George DT, Gilman J, Hersh J, et al: Neurokinin 1 receptor antagonism as a possible therapy for alcoholism. *319:1536-1539*, 2008.
- 13) Ginsberg GS, Burke TW, Febbo P: Centralized biorepositories for genetic and genomic research. *Journal of the American Medical Association* 299(11):1359-1361.
- 14) Heilig M, Egli M: Pharmacological treatment of alcohol dependence: target symptoms and target mechanisms. *Pharmacology and Therapeutics* 111:855-876, 2006.
- 15) Hyman S: Can neuroscience be integrated into the DSMV? *Nature Neuroscience* 8:725-732, 2007.
- 16) Institute of Medicine: Broadening the Base of Treatment for Alcohol Problems, National Academy Press, Washington, DC, 1990.
- 17) Kreek MJ: Impact of bidirectional translational research on treatment in addiction. *Clin Neuroscience Research* 5:123-139, 2005.
- 18) Kurtz E: Not God: A History of Alcoholics Anonymous, Hazelden Foundation, Center City, MN, 1979.
- 19) Li TK, Hewett BG, Grant BF: Alcohol use disorders and mood disorders: a National Institute on Alcohol Abuse and Alcoholism perspective. *Biol Psychiatry* 56:718-720, 2004.
- 20) Madon G, Hofman K, Kupfer L, et al: Public Health: Implementation science. *Science* 318: 1728-1729, 2007.

- 21) Mankoff S, et al: Lost in translation: obstacles to translational medicine. *Journal of Translational Medicine* 2: 14, 2004.
- 22) McGovern MP, et al: A survey of clinical practices and readiness to adopt evidence-based practices: dissemination research in an addiction treatment system. *J Subst Abuse Treat* 26: 305-312, 2004.
- 23) Moss H, Chen CM, Yi H: Subtypes of alcohol dependence in a nationally representative sample. 91:149-158, 2007.
- 24) O'Brien CP, Kampman KM: Opioids: Antagonists and Partial Agonists, in Galanger M, Kleber M eds., *Textbook of Substance Abuse Treatment*, Third Edition, American Psychiatric Publishing, Inc., Arlington, VA, 2004.
- 25) Offit K: Genomic profiling for disease risk: predictive or premature? *Journal of the American Medical Association* 299(11): 1353-1355, 2008.
- 26) Pearson T, Manolio T: How to interpret a genome-wide association study. *JAMA* 299(11):1335-1344, 2008.
- 27) Piquette-Miller M, Grant D: The art and science of personalized medicine. *Clin Pharmacol Ther* 81:311-315, 2007.
- 28) Pellegrino E, Thomasma DC: *A Philosophical Basis of Medical Practice: Toward a Philosophy and Ethic of the Healing Professions*. New York, NY: Oxford University Press; 1981.
- 29) Prochaska J, DiClemente C: Toward a comprehensive model of change. In WR Miller, and N. Heather, eds., *Treating Addictive Behaviors: Processes of Change*, New York, Plenum Press.
- 30) Scott JG, Scott RG, Miller WL, Stange KC, Crabtree BF: Healing relationships and the existential philosophy of Martin Buber. *Philos Ethics Humanit Med* 4:11, 2009.
- 31) Stetler CB, et al: Overview of the VA quality enhancement research initiative. *Implementation Science* 3:8, 2008.
- 32) Waldman S, Terzic A: Individualized medicine and the imperative of global health. *Clin Pharmacol Ther* 82:479-483, 2007.
- 33) Woodward B, Fortgang J, Sullivan-Trainor M, et al: Underdiagnosis of alcohol dependence in psychiatric inpatients. *Am J Drug Alc Abuse* 17(4):373-388, 1991.
- 34) World Health Organization: *World Health Report*, 2002. WHO, Geneva.

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