Recent developments in addiction therapeutics*

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New medications and new behavioral treatments for addictive disorders have been published over the past 20 years. In general it has been found that the best treatments for addictions are a combination of medication and counseling or psychotherapy. Each of the addicting drug categories has specific medications. All of these drugs have in common the activation of the reward system of the brain. All produce reward intensely but by different pharmacological mechanisms. Using animal models that predict response in human subjects, we have been able to increase our understanding of addiction and improve the results of treatment.

The treatment of alcoholism is a good example. The story is one of translation from animal models to successful clinical trials and now with genomic evidence that may refine patient selection and improve treatment outcome. The seminal discovery was that alcohol significantly activates the endogenous opioid system in some but not all animal and human subjects so that part of the reward from alcohol ingestion is mediated via opioid peptides. The evidence for this is that pharmacological blockade of opiate receptors reduces alcohol drinking in a dose related fashion and blocks the increase in dopamine in the ventral striatum associated with alcohol ingestion. Altshuler reported the dose-related effect of naltrexone on decreasing ethanol drinking in the 10 out of 21 Rhesus monkeys that self-administered alcohol. This report led to dose ranging studies in human alcoholics beginning in 1983 at the Philadelphia VA Medical Center and then a controlled clinical trial. Naltrexone was found to reduce alcohol craving and relapse to heavy drinking, but not necessarily produce total abstinence. The finding of an association between alcohol and opiates was met with skepticism in the 1980s (and a rejection of the report by the *Archives of General Psychiatry*) but the treatment results were perfectly replicated by O'Malley and colleagues. In an unusual scenario, naltrexone received FDA approval on the basis of two studies conducted by academia initially with VA and later NIAAA support rather than the usual pharmaceutical industry initiated studies.

The opioidergic mechanisms involved in alcohol reward have subsequently been elucidated in both animal models and human studies, but the molecular mechanism of alcohol induced opioid activation remains unknown. The opioid activation leads to increased dopamine in reward structures such as nucleus accumbens, but this dopamine increase is blocked by naltrexone pre-treatment. Presumably the perception of reward is also blocked and the animal ceases alcohol self-administration. Human alcoholics also report a reduction in expected alcohol reward in clinical trials and in human laboratory studies.

In the 12 years since naltrexone's approval, an opiate antagonist has been tested in 29 controlled clinical trials in unselected alcoholics. Most have shown a reduction in heavy drinking produced by the medication as would be expected if the alcohol reward were simply diminished. Total abstinence has been noted less frequently. While the majority of trials have shown significant benefits over placebo, the average effect size has

been described as “modest” and the medication has not achieved widespread use. As with the original study in monkeys, there is great individual variability. Some alcoholics show great benefits (and have remained on the medication for years) and others report no benefit. Some clinical measures have shown promise in characterizing a naltrexone responder: high alcohol craving and strong family history of alcoholism. Human laboratory studies of family history positive, non-alcoholic volunteers have demonstrated higher plasma beta-endorphin response and greater stimulation from alcohol which is blocked by naltrexone pre-treatment[8]. Thus the clinically important feature is not a unique effect of naltrexone on the opiate receptor. Rather, the pivotal variation is in the endogenous opioid (EO) response to alcohol. Those drinkers who have a large EO response have alcohol stimulation blocked by naltrexone, but drinkers (possibly alcoholics by a different mechanism) who lack a strong EO response to alcohol would notice no benefit from naltrexone.

A candidate gene approach has led to the latest advance. This is a reasonable strategy in an effort to understand naltrexone effects because naltrexone is very specific for opiate receptors. There are more than 25 identified variants of the gene that codes for the μ opiate receptor; thus this was a reasonable place to start looking. The Asp40 variant in the Anton et al report has several functional aspects, but perhaps the most clinically relevant is an increased stimulation effect from alcohol. At least one copy of this variant has been reported with a frequency of 20 to 25% in European Americans but with great racial and ethnic variability.

In a human laboratory study, volunteers with this allele reported greater subjective stimulation from a given ethanol blood level and in a more recent study of heavy drinkers, naltrexone blocked the increased stimulation of the heavy drinkers carrying the Asp40 allele.

Of greatest importance to the clinician faced with treating the devastating disease of alcoholism, a significantly greater response to naltrexone treatment was reported in a retrospective analysis of Asp40 allele participants in clinical trials when they were randomized to naltrexone treatment. The recent report by Anton et al replicates and extends that finding. The implications of these reports are powerful for informing clinicians on choice of medication. Such a clinically relevant bio-marker could have an important impact on the DSM classification system as described recently by Hyman. There is a remarkable convergence among pre-clinical models, human laboratory models and clinical trials where the circumstantial evidence for a sub type of alcoholism resulting from a genetic variation producing an EO system that is more sensitive to alcohol and to a specific pharmacotherapy. A note of caution is in order in that a reexamination of a sub-sample of participants who provided DNA samples in the multi-site VA trial did not find a difference in response by genotype. Nevertheless, there is sufficient pre-clinical and clinical data supporting this pathophysiolgical mechanism that a prospective study in which participants are randomized to naltrexone or placebo on the basis of genotype should be conducted. The results of such a study could change clinical practice so that selection of medication could be based on genotype rather than guesswork.

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