

## **A Novel, Unexpected Treatment for Alcoholism**

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An excellent example of a totally new approach to treatment originating in an animal model is that of the discovery of the efficacy of naltrexone and other opioid antagonists for the treatment of alcoholism. During the 1970s, self-administration of ethanol by rats and monkeys either by oral or intravenous route became available. This enabled researchers to experimentally manipulate factors that influenced self-administration and to test the influence of other drugs on this phenomenon. A breakthrough occurred in 1979 when Altshuler (Altshuler et al., 1980) first reported his findings in a small group of Rhesus monkeys that were selected for their willingness to self-administer intravenous alcohol. Prior to the alcohol session, the monkeys received either saline or one of three graded doses of naltrexone. The animals showed a clear dose-response effect, with naltrexone producing a suppression of alcohol self-administration. Subsequently the finding was replicated in rats and in vervet monkeys with oral self-administration of alcohol.

Opioid antagonists were originally developed for the treatment of heroin addiction, and there was absolutely no idea when they were first synthesized that they might be used to treat alcoholism. But the results from animal models were consistent and clear. Beginning in 1983, a group of researchers who studied both animal models and conducted treatment studies in humans obtained an IND to administer naltrexone to patients with alcoholism. At this time, the medication was not yet approved for heroin addiction. The first non-blinded studies utilized a dose of 50 mg, the same dose chosen for heroin addiction, and some but not all alcoholics reported loss of pleasure from alcohol. Later, a placebo controlled, double-blind trial in chronic alcoholics receiving intensive psychotherapy at the Philadelphia VA Medical Center was conducted (Volpicelli et al., 1990; Volpicelli et al., 1992). Half of the patients received

naltrexone and half received placebo. The results were consistent with the findings in the animal models: the patients randomized to naltrexone reported less alcohol craving, less reward from alcohol if they did drink, and a significantly lower relapse to heavy drinking. This study was completely based on animal models and had no pharmaceutical company funding.

The findings from the first study were predictable from the results in animal models but they were not accepted in the clinical community, possibly because they raised the issue of a similarity between alcoholism and heroin addiction. Indeed, the main hypothesis was that alcohol could activate endogenous opioid transmission, thus producing reward via some of the same pathways as heroin. Subsequent animal studies using microdialysis in the reward system (nucleus accumbens) showed that alcohol increases dopamine, which is blocked by pretreatment with naltrexone. In the 1980s, however, the linkage between opioids and alcohol was not generally accepted and thus only the Penn group conducted naltrexone studies in alcoholics. The pharmaceutical company that owned the drug for the treatment of heroin addiction did not wish to pursue the alcohol indication.

Beginning about 1990, the University of Connecticut Alcohol Center in collaboration with Yale attempted to replicate the Penn study and reported almost identical findings (O'Malley et al., 1992). Through a series of lucky coincidences, the data were eventually presented to the FDA and, after review, the treatment of alcoholism was added to the official indications for naltrexone. Thus a completely new treatment approach was developed from animal models and translated into a practical clinical intervention with no pharmaceutical support for the pivotal clinical trials. The value of the animal model in this situation is that it permitted the discovery of a novel mechanism of alcohol reward with important clinical implications. Since this discovery in animals and the subsequent early clinical trials, other opioid receptor antagonists have been

found useful in alcoholism, and an extended release depot version of naltrexone has been marketed that only requires one injection per month for treatment efficacy. The depot version is now FDA approved for both alcoholism and opioid addiction.

Since only a subset of alcoholics respond to naltrexone, a pharmacogenetic mechanism was hypothesized. An allele of the  $\mu$  opioid receptor gene has been identified as a marker for increased euphoria from alcohol that is blockable by naltrexone and a strong clinical response to naltrexone in alcoholism treatment trials (Oslin et al., 2003; Anton et al., 2006). A mouse model with a “knocked-in” human  $\mu$  opioid gene also shows an enhanced dopamine response to alcohol (Ramchandani et al., 2011). This treatment may become the first medication in psychiatry to be guided by genotype.

### References

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