Genes May Predict Response

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stand that none of these SNPs constitutes a "gene" for addiction, he said. However, some of them do seem to alter how the mu receptor functions. One such SNP, for example, tends to increase the receptor's binding affinity for β-endorphin.

Dr. Berrettini and his colleagues have been studying mu receptor SNPs in the context of heroin addiction. Though they have not yet identified any single variant that clearly shows an increased prevalence among addicts, compared with nonaddicts, they have found some interesting racial differences. "In African Americans, we've found some alleles in 10% of the population that we simply have not found in people of European ancestry," he said at the conference, cosponsored by the New York Academy of Medicine.

This underscores an important guiding principle for genomic research: When looking at the influence of small genetic variations on the risk of a given disease state, it is important to compare ill versus well people of the same racial and ethnic background.

Though Dr. Berrettini's team was unable to identify a specific mu receptor SNP that correlated with heroin addiction, Swedish researchers were able to do so. They found a variant called A118G that does seem to predict risk of heroin dependence.

Approximately 18% of Swedish opioid addicts had disease that is caused in part by this SNP.

Some researchers have suggested that the mu receptor may play a role in alcohol dependence since ethanol triggers a release of β-endorphin, the key ligand for the mu receptor.

Available data correlating SNPs in the mu receptor gene and alcoholism are highly variable; there are as yet no studies showing a clear association. However, variants in this gene may predict an alcoholic's response to treatment with naltrexone.

Dr. Berrettini and his group have done a series of studies looking at multiple mu receptor SNPs in alcohol-dependent individuals treated with naltrexone. In the subgroup of patients who had either the A/G or G/G variants of the Asp40 allele, only 10% relapsed after nearly 3 months of posttreatment follow-up.

Those with the A/A variant had very high relapse rates, and outcomes were no better for naltrexone than placebo.

What these data suggest is that response to this drug, which is a mu receptor blocker, may be largely determined by genetic variants in a specific receptor.

This type of research is opening up the possibility of designing treatment protocols based on an individual's genetic predispositions.

Dr. Berrettini estimated that 25% of the alcoholic population is either homozygous or heterozygous for the G allele, and it predicts better response to naltrexone.

Those who are homozygous for the A allele do poorly on this drug. "We'd like to do a treatment study where we randomize based on mu allele genotype," he said.

Though still in its early stages, this type of research is opening up the possibility of designing treatment protocols based on an individual's genetic predispositions and likelihood of responsiveness to specific medications.

In other words, individualized therapy based on pharmacogenomics may soon become the standard of care.

The technology to screen for SNPs is very well developed, and the cost is rapidly decreasing. "It is definitely possible to do SNP testing in a community hospital setting, and insurance will even pay for some of this," Dr. Berrettini said.

"The biggest challenge right now is to make clinical sense of the massive amount of new information we have about the human genome." ■

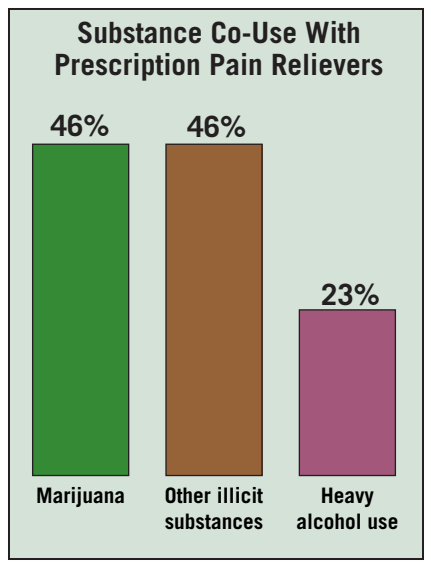
Dual Abuse Concerns May Hinder Buprenorphine Tx

BY DIANA MAHONEY
New England Bureau

CHICAGO — The fear that opioid-addicted patients may co-use other substances while receiving buprenorphine therapy may be keeping some physicians who are authorized to prescribe the drug for opioid addiction from setting up office-based treatment programs, according to LeChauncy Woodard, M.D.

Since October 2002, physicians have been allowed to apply for waivers of the special registration requirements defined in the Controlled Substances Act to prescribe buprenorphine in treatment settings other than a traditional opioid treatment program.

"However, physicians have been reluctant to embrace this treatment option, possibly due to concerns regarding use of other illicit substances among patients who abuse pain relievers," said Dr. Woodard of Baylor College of Medicine, Houston.



To estimate the prevalence of substance co-use among abusers of prescription analgesics, Dr. Woodard and her colleagues reviewed data from the 2000 National Household Survey on Drug Abuse, which showed that about 2.9% of Americans reported nonmedical use of pain relievers during the prior year, and 93% of those pain relievers were opioid analgesics.

Among users of prescription pain relievers, 23% reported heavy alcohol use, 46% reported using marijuana, and 46% reported co-using other illicit substances, Dr. Woodard reported at the annual meeting of the Society of General Internal Medicine.

Heavy use of alcohol was defined as having five or more drinks five times within the month prior to the survey. Rates for use of marijuana and other illicit substances were based on use during the year prior to the survey.

The investigators used logistic regression analysis to identify demographic factors associated with substance co-use in this population. The predictors considered were age, sex, race, education, employment, household income, veteran status, and metropolitan statistical area. "Controlling for other predictors in the model, age, race, and marital status were all broadly associated with heavy alcohol, marijuana, or other illicit substance co-use," Dr. Woodard said.

People aged younger than 50 years were significantly more likely to be co-users of all three types of substances than were those older than 50; white individuals were significantly more likely to co-use all three types compared with individuals of other races/ethnicities; and single people were significantly more likely than were those who were married to co-use all three types.

Men were significantly more likely than were women to co-use heavy alcohol and marijuana, and college-educated individuals were significantly more likely than were their less-educated counterparts to co-use the other illicit substances. ■

Legal Drugs Largely Behind Utah's Rise in Drug-Poisoning Deaths

BY MIRIAM E. TUCKER
Senior Writer

A striking rise in drug poisonings in Utah between 1991 and 2003 was largely attributable to medications that can be prescribed legally, the Centers for Disease Control and Prevention said.

Methadone and other prescription narcotics accounted for most of the tripling of the rate of "nonillicit" drug-poisoning deaths that were unintentional or of undetermined intent, from 1.5/100,000 population in 1991-1998 to 4.4/100,000 in 1999-2003.

During the 12-year period, the number of Utah residents dying from all drug poisonings increased nearly fivefold, from 79 (4.4/100,000) in 1991 to 391 (16.6/100,000) in 2003, the CDC said (MMWR 2005;54:33-6).

During 1991-2003, a total of 2,396 drug-poisoning deaths were identified in Utah's centralized medical examiner database.

Of those deaths, 947 were caused by illicit drugs only, 1,277 by nonillicit drugs, and 172 by a combination of the two. Alcohol was not considered a drug in this analysis.) The largest increase in annual drug-poisoning deaths—from 55 in 1991 to 237 in 2003—was attributed to nonillicit drugs, the CDC reported.

Methadone and other prescription narcotics accounted for most of the tripling of the rate of 'nonillicit' drug-poisoning deaths.

Among the deaths attributed to nonillicit drugs during 1991-2003, a total of 733 were classified as unintentional or of undetermined intent. Of these, the highest death rate was among adults aged 25-54 years.

The rate was higher for men than for women, although the percentage increase from 1991-1998 to 1999-2003 was greater among women.

Similarly, more deaths occurred in urban than in rural areas during both periods, but the increase was greater in rural areas And, although death rates rose substantially for people in all body mass index categories, rates were substantially higher during 1999-2003 among overweight (5.26/100,000) and obese individuals (14.25), compared with normal-weight people (3.61).

Comparing the two time periods, the average number of deaths attributable to methadone increased from 2 to 33 per year, while deaths attributable to other prescription narcotics—principally oxycodone and hydrocodone—increased from 10 to 48 per year.

From 1991-1998 to 1999-2003, the proportions of those deaths that involved alcohol decreased from 33% to 20%, while deaths due to antidepressants dropped from 15% to 7%.

During 1997-2002, Utah had an increase in the distribution of many of the prescription drugs implicated in these deaths, including methadone, but that rate of increase was surpassed by the rate of increase in poisoning deaths attributed to them. ■