

# Target 'Cellular-Level' Activity in Dependence

BY RENÉE MATTHEWS

BETHESDA, MD. — Chemical dependence as a result of drug abuse occurs at the cellular level because of neurochemical dysregulation, and an evidence-based understanding of these chemical dynamics and of the circumstances that drive a person to abuse drugs could yield a more comprehensive and effective approach to treatment.

"Chemical dependence is a disease of the brain caused by genetic vulnerability as well as exposure to a drug, and possibly other environmental factors such as trauma and family influence," said Carlton Erickson, Ph.D., a researcher in addiction science at the University of Texas at Austin, at the annual conference of the Association for Medical Education and Research in Substance Abuse.

Specifically, dependence occurs because of a neurochemical dysregulation

ways to a drug leads to changes or adaptations in nerve function, which are known as neuroadaptations. These changes reach a threshold, leading to compulsive drug use over which the individual has impaired control, Dr. Erickson suggested. "The main symptom of chemical dependence is impaired control over the use of a drug, and the patient perceives this as a basic need for the drug."

The mesolimbic dopamine system is a

grouping of axons that extends from the brain's amygdaloid region to the frontal, prefrontal, and anterior cingulate cortices that regulate feelings of pleasure. The different regions of the brain along the route of the MDS are governed by certain neurotransmitters, for example, dopamine (pleasure) in the ventral tegmental area, amygdala, hippocampus, and nucleus accumbens; serotonin (cravings) in the hypothalamus; and gam-

ma-aminobutyric acid (GABA; sleepiness), also in the nucleus accumbens. Some addictive drugs such as cocaine, LSD, or benzodiazepines match up with and target certain neurotransmitters (dopamine, serotonin, and GABA, respectively), which might explain why some people have a drug or drugs of choice, Dr. Erickson said. "Multiple dysregulation could explain a person's dependence on several drugs," he added.

**'Chemical dependence should be treated by positively affecting the abnormal brain function—dysregulation—to reduce the need for the drug that is being abused.'**

of the mesolimbic dopamine system (MDS), which also is called the medial forebrain bundle or the pleasure or reward pathway because of dopamine's association with mood regulation, motivation, and reward, he said.

"We assume that a certain genetic propensity together with drug use can lead to dysregulation of the MDS neurotransmitter processes; that is, when people use a particular drug, it 'connects to' or 'matches' the transmitter system that is not normal" and disrupts the cellular-level functioning of the pathway. This connection occurs because drugs typically act on a single neurotransmitter system, and those systems are particularly vulnerable to the specific drugs.

Continued exposure of the MDS path-

## Opioid Addiction Treatment Booklets

Three free booklets on medication-assisted treatment for opioid addiction are available from the Substance Abuse and Mental Health Services Administration. The booklets—two for patients and one for families and friends—provide information on medication options, proper use of medications, common side effects, and the recovery process. "The Facts About Naltrexone for Treatment of Opioid Addiction," "The Facts About Buprenorphine for Treatment of Opioid Addiction," and "Medication Assisted Treatment for Opioid Addiction: Facts for Families and Friends," can be ordered at <http://ncadistore.samhsa.gov>. ■

**NEW INDICATION**

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**WARNING: AVOID USE IN PREGNANCY**

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, MICARDIS® (telmisartan) tablets should be discontinued as soon as possible (See Warnings and Precautions).

- MICARDIS is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.
- MICARDIS is indicated for reduction of the risk of myocardial infarction, stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors.
- High risk for cardiovascular events can be evidenced by a history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin dependent or non-insulin dependent) with evidence of end-organ damage. MICARDIS can be used in addition to other needed treatment (such as antihypertensive, antiplatelet, lipid-lowering therapy, etc).
- Studies of telmisartan in this setting do not exclude that it may not preserve a meaningful fraction of the effect of the ACE inhibitor to which it was compared. Consider using the ACE inhibitor first, and, if it is stopped for cough only, consider retrying the ACE inhibitor after the cough resolves.

- Use of telmisartan with an ACE inhibitor is not recommended.
- Volume depletion and/or salt depletion should be corrected in patients before initiation of therapy or start treatment under close medical supervision with a reduced dose, otherwise symptomatic hypotension may occur.
- In patients with impaired hepatic function, initiate telmisartan at low doses and titrate slowly.
- Monitor carefully in patients with impaired renal function, especially in patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (eg, patients with severe congestive heart failure or renal dysfunction); treatment of these patients with ACE inhibitors and ARBs has been associated with oliguria and/or progressive azotemia and, rarely, with acute renal failure and/or death. In patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen may occur.
- Dual blockade of the renin-angiotensin-aldosterone system (eg, by adding an ACE-inhibitor to an ARB) should include close monitoring of renal function. Use of MICARDIS with ramipril is not recommended.

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Other pairings between addictive drugs and neurotransmitters include heroin and endorphins, nicotine and acetylcholine, alcohol and glutamate and substance P, and marijuana and endocannabinoids.

If chemical dependence occurs at the cellular level, then it would make sense that the treatment should also work at the cellular level, Dr. Erickson said. "Drug abuse is seen as a problem that needs to be solved through education, coercion, punishment, environmental change, or maturation, whereas chemical dependence should be treated by positively affecting the abnormal brain func-

tion—dysregulation—to reduce the need for the drug that is being abused," Dr. Erickson said at the conference, which was sponsored by Brown Medical School.

Both abuse and dependence are serious conditions, and both need to be addressed, but they are not the same, he added. Drug abuse is volitional (person has control over drug use), but chemical dependence is an involuntary brain disease, so each requires a different treatment strategy.

Among the current options for initiating recovery are the traditional 12-step programs, which encourage abstinence;

counseling for behavioral modification; cognitive-behavioral therapy (CBT) and primary care management; and medical treatment, which could include using detoxification medications or medications that enhance abstinence (at the cellular level), such as reward blockers, and anticraving medications such as methadone, buprenorphine, and vaccines.

One could argue, Dr. Erickson said, that behavioral therapies probably also change brain chemistry. "In other words, [during behavioral therapy] the MDS dysregulation begins to move back toward normal. It cannot be totally nor-

malized, just "pushed back" toward normal, in much the same way that medications change brain chemistry."

Although there are no direct brain imaging studies that show that this happens in dependence treatment, plenty of imaging research shows that psychotherapeutic methods such as CBT change brain function. Thus, "talk therapies" probably change brain function in a positive manner to help overcome dependence, he explained. ■

**Disclosures:** Dr. Erickson had no conflicts of interest to report.



## KE, OR DEATH FROM CV CAUSES

ACE-I: Angiotensin-converting enzyme inhibitor. MI: Myocardial infarction. CV: Cardiovascular. ARB: Angiotensin receptor blocker.

### **MICARDIS 80 mg is now the only ARB proven to reduce CV risk in high-risk patients who are unable to take an ACE-I.**

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\*High risk is evidenced by a history of coronary artery disease, peripheral arterial disease, stroke, transient ischemic attack, or high-risk diabetes (insulin dependent or non-insulin dependent) with evidence of end-organ damage.



**DO MORE TO REDUCE CV RISK.**

**References:** 1. Micardis Pl. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2009. 2. Teo K, Yusuf S, Sleight P, et al; and the ONTARGET/TRANSCEND Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *Am Heart J*. 2004;148:52-61. 3. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; and the HOPE Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145-153.

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