RESPONSE: ANTICIPATING NEW MEDICATIONS

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Lawrence DeMarzo: My agency, House of the Crossroads, like other drug-free community-based agencies, has historically chosen not to use medications in its treatment regimens. That is changing now, through our involvement in NIDA's Clinical Trials Network and our acquaintance with literature like Dr. Kampman's article (Kampman, 2008).

Much has changed since we started Crossroads. We know a lot more about addiction and treatment than we did 40 years ago. Although the agency is not using any medications yet, we are considering implementing a methadone-to-abstinence model for heroin abusers. Methadone appeals to us, because we have seen that it works, and because it seems to be a service line that produces stable utilization and retention, which a fee-for-service structure needs to generate revenue to cover the cost of care. I was impressed and encouraged by Dr. Kampman's positive outlook on the potential for medications to treat stimulant abuse. The drugs in this class, particularly crack cocaine and methamphetamine, have had the most devastating effects on our community and present the greatest challenge to us in terms of providing effective treatment.

Michael Bogenschutz: At our large, outpatient substance abuse program at the University of New Mexico, we generally try to treat drug abusers pharmacologically to help them through detoxification. We used amantadine for a number of years and have also used a number of other medications—including baclofen, disulfiram, and propranolol—based on what has seemed most promising at the time. With each of these medications, some patients will say that it made a big difference. I believe they help, but I wonder how much. The empirical findings for all of them are still equivocal—some promising results on the one hand, but without substantiation in large clinical trials. On the other hand, I am sure that the structure and support we supply along with medications contribute significantly to our patients' recoveries.

John Roll: Do you think those medications you use affect addiction directly or do they affect co-occurring psychiatric conditions that may be enabling or facilitating the drug use?

Bogenschutz: I think they affect addition directly. These patients are in our primary addiction treatment program, and they may or may not have co-occurring disorders. We target early withdrawal symptoms, like craving, and hope to normalize the function of a person's brain. Disulfiram or gamma-aminobutyric acid (GABA)-ergic medications can also affect the reinforcement value or effects of cocaine or methamphetamine.

Roll: One point that I think bears highlighting is that medications compensate for some of the reinforcing effects of drugs, but only some. At one level, drugs reinforce abuse because of their pharmacology, and it makes perfect sense to target those aspects of reinforcement with pharmaceutical interventions. However, drugs also accrue reinforcing efficacy by other means, like the associations of a drug-using peer group. I've heard anecdotal evidence that some women initiate use of methamphetamine to take advantage of its anorectic properties and control weight. Sex workers have told me that they could never do their job without drugs, so they have an economic incentive to continue using them. Medications don't directly modify these sorts of reinforcement and therefore may not constitute treatment all by themselves.

Bogenschutz: A good example of that point is the experience with naltrexone. When naltrexone was first released, many thought it would be 100 percent effective for opiate dependence, because it functions like an antidote for heroin. However, in the real world, naltrexone has had only a small impact on opioid dependence treatment. Most patients simply won't take it; it causes dysphoria in opiate abusers, and it doesn't decrease craving. Patients who do take it can simply stop if they want to resume heroin use. We would likely face similar problems with some of the medications Dr. Kampman discusses, particularly the cocaine vaccine.

DeMarzo: I have heard Nora Volkow, NIDA's director, make the case that developing effective medications to treat stimulant addiction is an avenue to reducing the stigma of addiction and legitimizing addiction treatment services. That makes sense to me, and it's one of the reasons I find this research exciting.

Grounds for implementation

Bogenschutz: At this point, we don't have a good estimate of how effective any of the medications being developed to treat stimulant abuse are going to be. However, any efficacy that's even just a little better than marginal is good enough to warrant implementing a new medical intervention for this disorder. Consider Food and Drug Administration (FDA) standards as to what constitutes a clinically significant benefit in the addiction field. There are FDA-approved medications for alcohol dependence, like naltrexone, with effect sizes of 0.2 or 0.3. At first glance, that doesn't sound like much,

but it's not atypical for medications that treat chronic illnesses. If many people are treated, the total benefit still could be quite large. All of the medications currently in the drug treatment armamentarium have relatively small effect sizes. The reason goes back to John's comment: The pharmacological effects of drugs are only part of what is going on in addiction. Social learning, conditioning, and biopsychosocial factors all contribute, too.

Roll: Those factors vary from person to person. Before applying any approach to an individual patient, treatment providers need to do a functional analysis to see what may or may not work. I am not an M.D. or a pharmacist, but I am not aware of any medicine that is 100 percent effective for any condition. I don't know that there will ever be one medication that helps everybody stop using drugs.

Bogenschutz: Safety is another primary concern in deciding whether to implement a medication intervention in a program or use it with a particular patient. Especially when using a medication off-label, that is, for a purpose other than the FDA-approved ones, the burden is on prescribers to show they have adequately considered the potential safety issues and have done everything to minimize the risks. Some of the medications Dr. Kampman discusses don't require anything more than monitoring liver enzymes, reviewing patient history, and/or performing a physical exam to rule out cardiac disease or similar conditions. Others can pose significant risk. Disulfiram is perhaps the most promising medication mentioned in the article; however, it's also probably the most dangerous, because the alcohol–disulfiram interaction can be fatal, and because very rarely, there have been cases of patients developing liver failure so severe that they needed liver transplants. Gamma-vinyl GABA raises concerns about visual field defects. Modafinil and the anticonvulsants are probably pretty safe, but even they have sedative effects, neurological side effects, and potential hepatotoxicity and other organ effects.

Roll: I'd add that you need to have a discussion with the patient to inform him or her that you're recommending an off-label use of the medication and to enumerate potential risks. Otherwise, most patients will assume that your prescription is an evidence-based practice, though the evidence is not necessarily there.

Bogenschutz: Absolutely. In sum, from my perspective, clinical judgment has to be the primary basis for implementing or not implementing use of these medications at this time. The evidence isn't strong enough for a program to make a guideline that patients should receive any of them. If a program does decide to use one, however, it will need to create guidelines for using it safely. With disulfiram, for example, the guideline would require clinicians to make sure that people are clearly informed that the medication is being used off-label, that screening for adverse effects is appropriate, and that people get the information they need regarding the risks of using alcohol or cocaine while on the medication.

DeMarzo: Cost is a big issue for us. If an intervention is too expensive, we simply won't use it. If we, as a community-based agency with limited resources and experience with medical interventions, decide to implement a medical intervention, we have to consider infrastructure, training, licensing regulations, and staffing issues. One of the greatest challenges with the transfer of research to practice is that researchers have limited resources that often do not afford the opportunity to build front-end, cost-benefit analysis into the studies.

Roll: As a researcher, I think there is so much that is exciting to be learned about pharmaceutical approaches to stimulant abuse that I would hate to see us become overly concerned with cost at this stage. Once we get a better feel for which approaches really work, how, and for whom, cost will become a much more salient issue.

Bogenschutz: Although cost-benefit is important on a systems and program level, cost generally drops out of the equation at the clinical level. The formulary or the insurance company tells you what the patient can and can't have. The clinician's primary role with regard to these medications is to weigh the benefits and potential adverse effects. The overall clinical challenge is to get the most out of the mix of marginally or modestly effective treatments that we have available for stimulant abuse. Treatment providers will have to figure out optimal dosage and duration for pharmacological treatment, and what kinds of psychosocial components should be used with the particular medication or vaccine.

The decision to use a medication or particular behavioral intervention will probably also depend on individual patient characteristics, such as addiction severity, gender, other substances abused, psychiatric comorbidity, and so on. Sometimes these subgroups can be identified in the analyses of larger trials, which may prompt subsequent trials of those subgroups, as was done with propranolol. There's an interesting secondary analysis of the COMBINE study data for naltrexone showing that efficacy in that trial was limited to people who had a particular mu opioid receptor polymorphism (Anton et al., 2008). Such information may allow us to match treatment plans to particular subgroups or individuals and thus magnify the effects of what are now marginally effective treatments.

Roll: I think we are just starting to figure out how to incorporate pharmaceuticals into treatment for stimulant abuse, and Dr. Kampman has made a good start. He suggests a strategy of matching medications to the phase of treatment, such as initiation and maintenance, and I think one might do the

same for behavioral psychosocial approaches, though it's complicated to match a psychosocial or behavioral intervention to a particular medication. Some research has shown a synergy between voucher-based reinforcement therapy and pharmaceutical treatment, but that's just one of many possible combinations.

Bogenschutz: As behavioral interventions go, the findings are most robust for contingency management. However, that approach is used infrequently, because insurance companies and the public sector are reluctant to fund it, and many of the treatment agencies may be reluctant to implement it.

Roll: If the cocaine vaccine should turn out to be effective, it will need to be delivered in the context of a thoughtful psychosocial behavioral platform as well. Even more than the medications, the vaccine will raise bioethical concerns about who should receive it, whether anyone should be compelled to receive it, and if so, under what circumstances.

REFERENCES

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