

You'll Get No Kick From Cocaine

What if there were a safe and lasting way to block the high that users get from cocaine, no matter what form—injected, snorted, or even the potent inhaled drug called crack?

That possibility comes a little closer this summer, when Hopkins begins trials of a prototype cocaine vaccine on 50 men and women who actively use the drug but insist just as actively that they want to quit.

Some 300 will participate nationwide.

Stopping cocaine's effects completely could bring a sea change in recovery strategies, the researchers say. But even if the vaccine merely blunts the high, that might tip the balance enough to make existing tactics more effective. The potential is there; it's just waiting to be realized.

Led by **Maxine Stitzer**, Ph.D., and **Andrew Tompkins**, M.D., with the Behavioral Pharmacology Research Unit, the Hopkins team is one of six nationally to conduct phase II trials of the TA-CD vaccine. Ideally, the vaccinations will prompt subjects' immune systems to create useful antibodies—those able to pick off cocaine molecules before they cross the blood-brain barrier to stimulate dopamine-based reward circuits in the brain.

The upcoming studies follow a decade of animal research and then a sentinel inpatient vaccine study of cocaine-users. "Even before it appeared in a journal last fall, the results of that inpatient trial caused a stir in the research community," says Stitzer. "It was the first time that a treatment substantially reduced the subjective effects of cocaine. After literally *years* of seeing negative trials, this would be hard to overlook.

"That said," she adds, "we know there are still challenges." The anti-cocaine antibody levels, for example, fade within a year, making booster shots necessary. In a larger outpatient study, just half of fully inoculated people produced enough antibodies to dull cocaine's effects. Still, Tompkins points out, the possibility of helping even that many motivated cocaine users is highly significant for a life-sinking illness that affects millions.

He also takes heart in the potency of the vaccine for those who are affected by it. "It appears to damp down even crack cocaine," Tompkins says, "which travels the fastest to the brain."

"It's time for a new approach," says Stitzer. Unlike other addictive drugs, cocaine has danced away from 30 years of concerted searching for a medication to stop dependence. The same is true for its amphetamine cousins and the other stimulants. There's no methadone-equivalent, as exists for heroin or other opioid addictions. Much of the problem, Tompkins says, stems from the stimulants' intimacy with normal brain circuitry: "That makes it difficult to find an agent that blocks the drugs while leaving important brain function intact."



Addictions researchers Andrew Tompkins and Maxine Stitzer see vaccines' potential as part of a wave of change in addictions treatment. "There's no magic bullet," says Stitzer, but patients could go longer between visits and the biology is more strongly on their side.

For the upcoming trials, it will take several injections of vaccine to get the anti-cocaine antibody titer as high as necessary. So five injections are scheduled at intervals, as is antibody sampling. The physiology and safety will still be under study, but researchers' eyes will linger longest on the urine tests and written surveys that would flag a hoped-for drop in subjects' cocaine use.

If the trials are successful, says Stitzer, the vaccine would then be a candidate for FDA approval, and then, ideally, tailored to community use. ■

For information: 410-550-5044

Staying the (Vaccine) Course

For want of a nail, the shoe was lost. Shakespeare went to great lengths to show the need for attention to detail—finally it's



a kingdom gone, thanks to a lame horse.

But the researchers testing an anti-cocaine vaccine (story, left) are well aware of details that, ignored, could derail their trials. High on the list is compliance. Asking cocaine-dependent subjects to come for two weeks of screening, then monthly visits including tests and injections and then a follow up two weeks later—is a lot, even if they appear highly motivated.

"Asking anyone for that sort of compliance is a lot," says addictions researcher **Maxine Stitzer**. She's one of a national cadre of experts in motivation and contingency management—a field she describes as "providing incentives to help people adhere to regimens that are good for them." Stitzer's advisement has figured prominently in the study.

"Compliance is a broad, common problem in medicine," she says, whether it's taking a full course of antibiotics or keeping a symptom log. People in drug abuse programs aren't an exception.

So well before start of the multisite trials, Stitzer and colleagues knew preliminary research was in order. They simulated the cocaine-vaccine trial using a different vaccine that participants needed—one for hepatitis B.

For some in the study, the researchers offered an encouragement common in addictions treatment—in this case, a "draw bowl" containing 500 tickets, half exchangeable for prizes or gift cards. Others were simply asked to stay the course. The result? A full three-quarters of those with access to the bowl received all their scheduled injections. For the comparison group, it was less than half. Stitzer was especially surprised as the differences opened up later in the 6-month program when motivation starts to flag.

Incentive programs aren't whimsical. They take a fair amount of forethought. "They're also consistent with principles of behaviorism," Stitzer adds, "and could play a significant part in keeping people coming long enough to finish a course of vaccines." ■

Adding Insult to Injury

When chemo or radiation alter children's thinking.

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Balancing Act

Giving families, planning and therapy more equal weight helps with teen mood disorders.

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Cyber Psych

New online mood assay bumps up compliance.

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Brain Interrupted

All the while teens are lolling in Starbucks, drinking lattes, their brains are being pruned. Unneeded neurons fade away, leaving room for the great meet-and-greet of white matter that develops as fibers from remaining cells make new contacts. Millions of them.

The changes underlie the switchover to the quickened mental processing, the ability to multitask and plan that mark adult thinking.

"It's an especially unfortunate time, however, to be treated for a brain tumor," says pediatric neuropsychologist **Mark Mahone** who knows whereof he speaks. For some two decades, Mahone and his colleagues have assessed cognitive and other abilities in children at various ages, after they've received combinations of surgery, chemotherapy or radiation for brain tumors or leukemia.

It's the sort of work that, in the 1980s, led Hopkins—and then other hospitals—to phase out whole-brain radiation for children as a primary leukemia therapy.

Today, radiation use is far more judicious, thanks to the sharper focus and lowered dosage that new technology allows. Chemotherapy is also advancing. But, says Mahone, he still wrestles with basic questions. Mahone is with both Hopkins Psychiatry and the Kennedy Krieger Institute.

The literature on children receiving

chemotherapy or cranial radiation isn't conclusive, he says. Young patients vary greatly—by age, background, overall health, their tumor's location, its aggressiveness, therapy dosage and its route of delivery, presence of seizures or other complications—and that makes large-scale research on identical groups a challenge. "Studies can also be more complicated than in adults," he says, "because children's brains are developing." Still Mahone and colleagues advance understanding.

"I couldn't tell you today, for example, if a particular 12-year-old child receiving radiation for a brain tumor would definitely suffer from a loss of skill in, say, three years."

But Mahone's research on radiation shows a pattern that guides prediction: After an initial, not-unexpected dip in cognitive and motor function, patients gain some skills back roughly a year later. "But when you follow children farther out," he says, "you see that, unlike with chemotherapy, there's a continued skill loss in some of them."

"Brain growth is essentially interrupted," says Mahone, and effects can surface with each new developmental demand. That's

why treatment at puberty is especially fraught with decisions.

"Still, we have enough certainty to give a family a sense of what struggles lie ahead and what we can do to help, Mahone says.

"My clinical role is in assessment," he explains. "It's testing to be able to tie a child's medical and neurological condition to what he or she can do bodily, mentally and socially. If we know, for example, that motor skills, working memory or attention are the main issues, we have behavioral approaches that can make a difference."



Mark Mahone has a library of over 400 tests—some his own—to flag children's problems post-therapy for cancer.

A child who's had chemotherapy in first grade might show memory problems, but it's not so bad because nobody expects him then to remember all he's read. It will be a problem when he gets to fourth grade, though, and Mahone can alert both family and the rehab team to begin working on memory strategies.

A family's relief at having understanding and a plan, he says, is often almost palpable.

For information: 443-923-4442.

Adolescent Mood Disorders: More Than Meds

Anyone who's raised teenagers bears witness to the moodiness and angst that can surge during adolescence and into young adult years.

Being in that age group with depression or bipolar disorder, however, brings extra layers of challenge, says psychiatrist **Elizabeth Kastelic**, who directs Hopkins' Adolescent and Young Adult Mood Disorders Inpatient Service. Then, teenage moodiness and irritability become intense, even debilitating, and invite a host of other problems, from difficulty concentrating to a chronic irritable state that can be overwhelming.

Under Kastelic, however, the service has evolved tactics to provide patients with skills for managing such symptoms. "With the right tools," she says, "they learn to cope with their illness at what's often a high-stress time for anyone, well or mood-disordered."

But before newly admitted patients can begin to think about disposition, they must first reach a benign-enough mood. So a clinical team works with them early on to fine-tune medication. At group meetings led by nurses and occupational therapists, patients learn about their illness. They also practice problem-solving, communication skills and the coping mechanisms that can manage symptoms and help prevent relapse.

During a therapy session, for example, a young woman might be led to realize that her constant lashing out at parents or friends in response to conflict or stress is really depression manifesting itself. "That leads us to discuss consequences of acting on this irritability," says Kastelic. "We'd explore how that makes the parents feel."

Asked to come up with healthier alternative behaviors, the patient might suggest requesting that the family take a 24-hour time-out from heated discussion.

Nurses and therapists also apply a behavioral activation approach—the idea that simply increasing activities in a patient's day, particularly enjoyable ones, aids recovery. It's not unusual in a mood disorder to withdraw from daily activities—school, work, social life—and have irregular sleeping and eating patterns.

"Depression," notes Kastelic, "can wreak havoc on routines of daily living." So patients spend time charting how they will spend their days after they are discharged.

Each day, Kastelic says, should have an anchor—a reason to get out of bed, like attending a class, working for an hour, even sticking to regular mealtimes. A critical part of the process, says Kastelic, is making a "pleasant events schedule"—



listing activities that a patient finds enjoyable and marking times to do them.

Finally, as patients leave the program, they write a safety plan: a list of tactics to apply if they notice symptoms returning. If a patient notices his mood declining or starts having thoughts of harming himself, for instance, his plan might be to first listen to music for 20 minutes. If his symptoms remain, he'll then talk to a parent. If that doesn't help, he'll call his doctor.

"It's a protocol," says Kastelic, "just as you'd

Antidepressants Useless? Far From It. Check the Study.

Last winter, a study in *JAMA* became a media wonder in part because of its message but also because of its ease of fitting into a sound bite: Antidepressants are no better than a placebo unless your depression is severe. As a result, “patient response has been intense,” says psychiatrist **Glenn Treisman**. “Every week they tell me *I read that these things don’t work.*”

Treisman is one of many who questions that study—and others with a similar theme. They’re suspect in the way they interpret data, he says. “The problem hinges on ignoring something researchers learn in Epidemiology 101. And we do that,” he adds, “at our peril.”

A full professor in psychiatry and internal medicine, Treisman is best known internationally for his care of psychiatrically ill HIV-infected patients. His work with this population from early in the AIDS epidemic has translated into expertise in depression, addiction, personality disorders and chronic pain.

It’s his insight on the workings of psychopharmacology—he has a Ph.D. in the field—that we tap here:

Q. These studies are dangerous, you say.

A. Ten to 20 percent of people with major depression died by suicide before widespread antidepressant use. Depression doubles your risk for cardiovascular death after a heart attack, stroke, HIV. I’d say discouraging people from taking good medication for depression is dangerous.

Q. So what’s the problem with the studies?

A. Deep down, it’s failing to recognize that there’s bias in the way we select people for drug trials. In early studies of antidepressants, we were very *exclusive*. We’d

use what’s called research diagnostic criteria (RDC) that made *sure* someone had major depression before entering a trial. It’s a bit like a surgeon being totally convinced someone has appendicitis before doing surgery. And in those settings, antidepressants are good: 75 percent of people get better.

But because major depression can be so deadly, and because we have no unequivocal test for it, we err on the side of overdiagnosis and treatment. We’ve become inclusive. The clinical criteria in our *DSM [Diagnostic and Statistical Manual]* for example, aim not to miss anyone who might have depression. But using inclusive *DSM* criteria for our trials, as we do today, means we include a lot of people with depressive symptoms who don’t have major depression. It’s just as, in the 1950s, some people had surgeries without having appendicitis when their surgeons weren’t sure.

Q. So?

A. What happens is that more people—the ones without the true depression the drug’s intended for—report feeling better. Between 1980 and 2000, for example, the placebo response in antidepressant trials jumped from 20 percent to 40 percent. And when you allow for a margin of error, it starts to look like there’s no difference between the drug and placebo. But that’s wrong. The antidepressants work for true depression, even if it’s mild.

Q. And your confidence comes from...

A. A critical review of new and older literature. My years as a psychiatrist. But if you doubt me, think of the evidence pharma companies have to present to the FDA. By the time firms get to the point of getting a new drug registered, they have tons of phase I and



“We’re so bound up in the DSM that people aren’t able to interpret the data anymore,” says Glenn Treisman. “That’s what’s happened in these studies.”

II trials and basic science showing these drugs work. They *know* they work. Registration trials are too costly for *mights* and *maybes*.

Q. You’re eager for a last word.

A. The take-home message is that doctors who prescribe need to be critical thinkers. Each patient is entitled to expert *tailored* treatment, not a recipe derived from the average response from the average clinical trial subject. ■

MOOD DISORDERS: FIRST PERSON

A Long Road to ‘Really OK’

*It’s rare to have someone volunteer to talk openly about a psychiatric stay in a hospital—rarer still when that person is in high school. But Ashley Lamphere, now 17, who suddenly found her body capable of severe depression and anxiety, also has unusual insight and a generosity of spirit.**

Here Lamphere tells how she experienced the Balance Program for Young Adults—an update on Hopkins’ already-respected inpatient treatment for that age group, but with a new emphasis on family involvement and on the transition back home.

I know it’s unusual, but when I was 14, I asked to go to boarding school. It seemed right to leave the school in Manhattan that I’d always attended, to try something new. But once I was there, things seemed to fall apart. I was anxious in a way I’d never been. I couldn’t focus. I was up entire nights without sleep. Seeing the school counselor didn’t help; things got worse.

What really worried me was that I wanted to hurt myself in odd ways—something I’d never felt before. Because my dad is bipolar, my mom was especially concerned about that. [Lamphere’s father shared his story with *Brain Wise* several years ago.] Luckily, mom knew to get help. I was diagnosed with depression and anxiety and given medication.

I agonized for two weeks about whether to return to boarding school—decisions are hard when you’re depressed—and though I felt conflicted, I went back to my old school with my close friends and support. I wasn’t well, though. Thoughts of hurting myself turned into casual thoughts of suicide. Then I started to add details.

[This led Lamphere to a week in a hospital. She was discharged but then, several weeks later, went back to a different hospital after she admitted collecting Advil. She was there a month.]

A pattern began to appear. I’d anticipate leaving the hospital so much that I’d feel better. But I see now that I didn’t know how to take care of myself when I got home. I couldn’t cope. Finally, in November—the night after I swallowed all of my medications and ended up going to the local hospital—my dad drove me to Baltimore. The next morning, I was at Hopkins, where he’d been helped, talking with Dr. Kastelic. [Psychiatrist Elizabeth Kastelic admitted Lamphere to a 4-bed service for young adults and teens. Meyer 4 also has an adult mood disorders section.]

What was different there? For one thing, I’d felt guilty about how I was feeling—like I was really just some hormonal,

angst-y teenager exaggerating things. But the doctors emphasized that my problem was real, largely chemical and out of my control. And seeing the very sick adults around me with the same symptoms I had convinced me of that.

I learned about coping mechanisms. And though I laughed at first at the worksheets we had to fill in, I still have them at home because they were so helpful. Having to list how I would spend my time, how to find my safety net were new to me. Being there helped me see the good things in my life and how to make use of them. I also learned to be more aware of my state of mind, how to recognize a downward spiral.

Dr. Kastelic asked about my family relationships. I know others my age who suffer from depression, and they all say their parents are a source of stress. So she asked to meet with me and my mom. We talked about the importance of support, of understanding. It was good for us both.

Now I’m back in school and looking at colleges. The past two years have had ups and downs, but I’m more realistic in expecting that and in not being bothered by it. They helped me rebuild my life. Now I’m really OK. ■

*Her parents and doctor are aware of our publishing this.



“A mood disorder is a disease you can treat,” Kastelic says, “It’s not who you are.”

have for any other medical illness.”

Basically, she explains, patients should leave the program understanding that their mood disorder is an illness. “It’s really a message of hopefulness. A mood disorder is a disease you can treat. It’s not who you are.” ■

For information: 443-287-3480.

Mood Indigo Online

Mood 24/7 is the only service of its kind to monitor moods for medical purposes.

A group of residents surrounded psychiatrist **Adam Kaplin** as he quizzed them on the best next step for a patient with bipolar disorder, a woman who'd been on lithium therapy less than a month. She'd emailed Kaplin: *My mood is just the same as when I started and I'm feeling a little foggy. What should I do?*

Half the residents said not to change a thing. The others voted to decrease the lithium dosage and schedule an office visit. But when Kaplin produced a graph (right) of the young woman's mood over the past three weeks, it took only 30 seconds for them to agree: Stay on the dose.

Clearly, the patient's present mood was stable and positive. She'd just forgotten how low she'd been a week earlier and how that felt. But the improvement was in black and white.

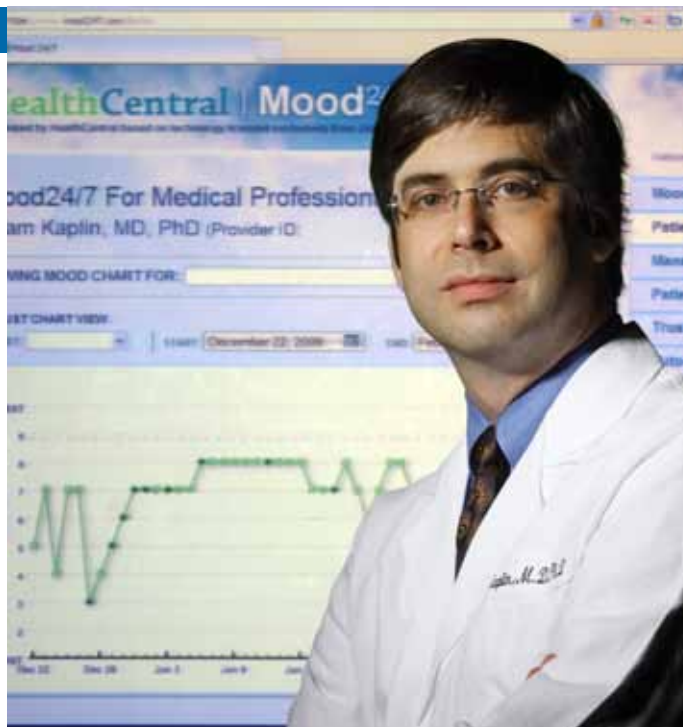
The episode typifies what Kaplin sees with Mood 24/7, a cellphone-based system for monitoring patients that's been in place half a year. "Patients take their own blood pressure; those with diabetes can check their own glucose," he says.

The value of regular monitoring isn't in question. Asking patients to assess mood daily and bring the chart to the next session is commonplace. Research confirms that the collected data can write a powerful signature of a patient's overall mental health. "The problem, however," says Kaplin, "is that compliance is terrible." Some studies rate it as low as 11 percent. "We've all seen patients sitting in the waiting room trying to backfill two weeks of data points.

"In mood disorders, concentration and memory are frequently impaired, yet, as clinicians, we still often rely on patients' retrospective recall to make decisions. I find that worrisome."

So Kaplin turned to texting. His Mood 24/7 system, created in conjunction with an established, online medical data-gathering service, offers daily mood-tracking through text messaging. It's the only cell-phone based service to monitor moods for medical purposes.

At an agreed-upon time, patients are texted, *What is your mood, on a scale of one (lowest) to 10?* The number typed-in becomes a data point on an online chart reached via a private ID and password. Patients may



"Our decisions are only as good as the information we have," says Adam Kaplin.

also authorize access for psychiatrists or therapists.

Benefits are the same as traditional assessments though they may come faster. Clinicians may be alerted sooner to a precipitous decline in mood that signals a patient's deepening depression. They may catch an upturn in suicide risk. And, as in the young woman on lithium, Mood 24/7 can already signal that medications look useful or may no longer be needed.

Is there a down side? Could the focus on mood itself alter how patients feel? Not to any extent that would outweigh benefits, Kaplin says. That's especially true since, early on, he and colleagues switched from using a depression scale to the more global mood score.

Kaplin's favorite testimonial comes from colleague Patricia Roy. "I'd been working with a chronically ill patient and hadn't made much headway in her treatment. She wouldn't keep a mood chart. Within a couple weeks of using [Mood 24/7] she had these lightbulb moments where she got what was going on with her mood disorder for the first time. I'd say she went from being a little bobblehead in a sea of emotions to being able to brace herself against the tide." ■

For information: akaplin@jhmi.edu or comment@mood247.com

A Site for the Memory-Perplexed

"We wanted to develop something that can be done at home, anonymously, that's easy to use and without cost," says neuropsychologist **Jason Brandt** of his new effort to give perhaps thousands of people worried about dementia a rough idea of risk.

What he devised had to be valid. It had to be sensitive enough not to mislead those at increased likelihood of dementia into thinking the status quo is fine when it isn't.

So about a year ago, Brandt launched the Memory Survey, a free, online dementia risk assessment (www.alzcast.org/memoriesurvey). Anyone can log onto the site, answer a series of questions about known dementia risk factors—traumatic brain injury, mood disorder, family history of dementia and the like—and take a short memory test.

Another web page lets a second party, such as a son concerned about his elderly father, take the survey.

The site then provides feedback. "We want to educate the public about dementia risk factors, to tailor what we tell each person, and to encourage people at high risk to see a competent clinician for a formal evaluation," says Brandt.

"If you take the survey, it becomes clear it's no substitute for seeing a specialist," he adds. Brandt, however, hopes the tool will identify more people in earlier stages of dementia and lead them to medical evaluation. "Early diagnosis is important," he says, "because existing therapies for Alzheimer's disease appear to work best when started early."

Right now, the memory test part of the survey is still being validated. Brandt has just finished evaluating the first 500 who've taken it. So far, what seems to predict poor memory performance are advanced age, hypertension, significant memory complaints and being male.

Now he's comparing results on the memory test and survey questions with "gold standard," in-person dementia evaluations by physician specialists.

Until that's complete, visitors to the site get "the most responsible information available," says Brandt, as an algorithm feeds back one of 24 tailored responses to the health history questions. ■

Hopkins BrainWise

This newsletter is published for the Department of Psychiatry and Behavioral Sciences by Johns Hopkins Medicine Marketing and Communications. 901 South Bond Street, Suite 550 Baltimore, MD 21231

Some of the research in this newsletter has corporate ties. For full disclosure information, call the Office of Policy Coordination at 410-223-1608.

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