

## Safely Medicating the Stork

**W**hen psychiatrist **Jennifer Payne** was thinking of starting a family, she made an appointment with her ob/gyn for reasons not so typical. A prudent woman, Payne wanted to see how early in a pregnancy she'd have to stop her regular asthma medication. "But my doctor laughed when I asked," she says. "Breathing and oxygen are *awfully* good for babies," Payne was told. And on the verge of motherhood, she found herself with a prescription change and an altered inhaler schedule rather than the expected drug holiday.

What happened to her should also be routine for pregnant patients at risk for mood disorders, says Payne, who co-directs Hopkins' Women's Mood Disorders Center. "But the misperception about medicating psychiatric illnesses unfortunately continues. People think, *just pull up your socks and go on*. And what patients see are big spreads in *Parade* about harming your unborn child if you take an antidepressant. No one writes those guilt-provoking articles when pregnant women take pills for high blood pressure," she adds.

Guilt may be the least of the damage that Payne wants to counter.

Pregnancy apparently doesn't change the risk of major depression in the general population. History of a mood disorder, though, raises it. So more than 60 percent of pregnant women who quit their antidepressants suffer relapse, according to one study. That drops to 35 percent at a lowered dose and around 25 percent for those who keep their pre-pregnancy dosages throughout.

Fewer studies exist for bipolar disorder. The consensus, however, is that stopping a mood stabilizer in pregnancy roughly doubles the risk of mood episodes, including



**"I almost always say that having a mood disorder doesn't preclude someone from having children," says Payne. "We're here throughout for support."**

depression and mania.

Moreover, mood-affected women often discontinue meds during the first trimester only to resume in the second, after a relapse. "These psychiatric flare-ups are far from benign for babies in utero," says Payne. Studies tie them to preterm delivery, low birth weight and increased risk of ADHD. And if the mother suffers postpartum depression—also more likely—babies are set for a rocky start.

So Payne is eager to help women at various points on the reproductive road—from preconception through breast-feeding. That's not always easy considering that the FDA hasn't approved mood disorder medications for pregnancy. As difficult: No long-term drug safety studies exist for exposed infants. All prescribing, then, is "off-label," putting a higher-than-usual premium on clinician experience.

So Payne lets her research and learning from the high volume of

patients she sees devise rules to sidestep problems. She knows, for example, that the mood stabilizer valproate has a small but real tie to fetal birth defects—a fact that fosters white-knuckle decision-making if that's the one drug that's kept a potential mother healthy. And she advises new breast-feeding mothers to take their antidepressants only at night after baby's asleep: Use formula or stored milk for nighttime feeds.

"If you get paralyzed by the lack of information, you end up harming patients," says Payne, "and we take an oath to do no harm. In these situations, you tell the parents, the pediatrician, the obstetrician what you know and what you don't. And you support the mother after her decisions. We're not about to abandon a patient—or her baby—if what she decides isn't what we would recommend."

*For more information: 410-502-7449.*

## Healthy Mom, Healthy Baby

What brought Amy Meacham\* face to face with her bipolar disorder was deeply unsettling: It involved police and restraints. But a positive twist, years later, has made Meacham a best case example for patients thinking of parenthood—so much so that psychiatrist Jennifer Payne presented the now-pregnant woman at a recent Psychiatry grand rounds.

Meacham grew up in a loving home where she very much mattered. Aside from a blip of depression in high school, she seemed on track. She graduated with honors from an Ivy League school, was teaching in graduate school, had a boyfriend. But stress and biology made other plans. At 26, she slipped into mania and psychosis. Wandering at dawn, she was picked up by police. One minute she felt at one with all of humanity; the next, she was restrained, sedated and ignored in a large inner city public hospital. "I was terrified," she says. "It took me six months to grasp reality."

The shock of that episode gave Meacham the bone-deep resolve to find and hold to the best therapy possible. She settled on lithium for mood stability and Wellbutrin to treat depression—a combination that allowed satisfying work and marriage.

But what pleased Payne most was that Meacham visited Hopkins for planning before pregnancy. Payne switched her off both drugs—lithium has a risk of making babies hypothyroid; Wellbutrin's in utero effects aren't clear—and onto Lamictal. The latter drug's original safe use for epilepsy throughout women's reproductive years means fewer surprises. "Also, you want to limit the number of drug exposures for unborn children," says Payne, "if only because nobody's studied combinations."

Lamictal was a good match for Meacham. Staying on it for a half-year before she was pregnant, as Payne recommended, wasn't difficult. A blood test during that waiting period marked a good baseline level for the drug, with continued monitoring during her first two trimesters.

Now well into pregnancy—she gives birth in September—Meacham has already discussed breast-feeding. Since all psychiatric medicine enters breast milk, she'll take steps to minimize exposure. Also, she'll stay on lamictal, a tactic so newborns avoid the bump of a switch.

"Healthy mom/healthy baby is our watchword," Payne says. ■

*\* To protect privacy, her name and some details are switched.*



### Likely Threesome

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# Tourette's, OCD, ADHD: Closer Together Than We Thought

**A** recent large study on the genetics of Tourette's syndrome has added clout to what many experts suspect: that underlying biology—common genes, most likely—can tie together Tourette's, obsessive compulsive disorder (OCD) and ADHD.

That doesn't mean all patients with Tourette's also have OCD and ADHD, says pediatric psychiatrist **Marco Grados**, who leads Hopkins' part of an international consortium. "But likely a third of children with Tourette's belong to a subset with all three disorders." And being aware of that, Grados says, makes therapy more precise. It also supports what's known of the pathology.

"We see child after child at our clinic primarily with the motor or vocal tics of Tourette's. But after a workup, you often find anxiety-based obsessive thinking and inattention with hyperactivity. Or perhaps they come with OCD and you see the other two." Children may be prescribed conflicting therapies. And parents are frustrated, says Grados. They've often shuttled kids from a hometown pediatrician who diagnoses one disorder, to a psychologist who says it's another, to a neurologist who finds yet a third.

It can be a confused family that comes to Hopkins.

The new NIH-sponsored work looked at more than 950 patients, siblings and parents from 220 families with Tourette's, as collected by the Tourette Syndrome Association International Consortium on Genetics. From his background in mathematics and genetic epidemiology, Grados saw the sense of using "latent class analysis"

on the large population. That's a statistical technique that cherry-picks groups of people from a mass of motley data. A result? Patients with all three disorders newly stood out.

A second analysis—calculate the odds of having family members with the triple problems—confirmed that if you have all three disorders, it's more than likely that relatives do too. Such "breeding true" cries out, *a culprit gene!*

"Perhaps"—and it's a big perhaps, Grados says—"we should think of this triple disorder as a single new one."

The study makes ideas about a common pathology more plausible. OCD, ADHD and Tourette's, it's believed, likely live in the large circuit that connects various parts of the brain's basal ganglia with the cerebral cortex. If, because of an errant gene, the loop is overactive or otherwise out of control, it makes sense that all three disorders would surface.

All three developmental disorders are marked by a lack of inhibition, whether it's not being able to control OCD's intrusive thoughts or Tourette's motor tics. It's also intriguing, Grados adds, that the three illnesses tend to fade after adolescence. "Sometimes one or another will just melt away," he says. Is it coincidental that Mother Nature's so-called maturity pathways—those descending from the reasoning cortex to lower regions like the basal ganglia—get stronger then?

More immediate, though, is the clinical value of seeing the disorders as a set. "Because treatments for all three diverge," says Grados, "prescribing becomes a careful balancing act." Tourette's for example, calls for medi-



**"Of all my work, this is the most forward-looking," Grados says of bringing insight to the three big childhood disorders where inhibition has flown away.**

cations that turn down dopamine. ADHD requires just the opposite with stimulants like Ritalin. "You can't just say, *the ADHD's the worst. I'm going to treat that and let the others ride.* That could aggravate the Tourette's."

"You put the pieces together," he says, "and things start to make sense." ■

For information: 443-287-2291

## A Current Approach to Depression Magnetic brain stimulation comes with potential and a research checklist.

A \$60,000 transcranial magnetic stimulation (TMS) system was recently unpacked in the Meyer 3 suite where it becomes the centerpiece of a new patient service opening this fall.

It looks like nothing so much as a very cushy dentist's chair with a calculator-size device on an attached adjustable arm. But TMS is out of the box in ways more than literal. And it offers a high-tech alternative for patients with deep, lasting depression.

TMS induces weak electric currents that excite targeted sites in the brain. Why that can ease depression is far from clear, says psychiatrist **Irving Reti**, who directs Hopkins' new Brain Stimulation Program. But having a safe and noninvasive treatment that, unlike medication, doesn't have whole-body effects is reason enough for making it available, he says. The understanding will come later, with his and others' work.

TMS was FDA-approved for clinical use last year as an alternate therapy for major depression in adult patients who've given antidepressants a valiant trial and not been helped.

"It's still a work in progress, though," Reti says. So Hopkins' use begins by sticking closely to the FDA guidelines. "The main question," he explains, "is efficacy." With TMS, relief from depression appears variable. For some, it's just short of god-from-a-machine; there are patients who report that their depressions

lift completely. Others see less effect. The benefit averages out, according to some 30 trials conducted worldwide, to about a quarter of patients reporting significant relief. Then follow-up antidepressants sustain it.

"There's a real need to be able to identify who's most likely to be helped," Reti says, "and we'll be looking for clinical predictors." The fact that TMS takes a time commitment—the recommended protocol is 40 minutes daily, five days a week for four to six weeks—underscores the need.

Safety, however, isn't in question. "The risk of seizures, which might be a concern, is exceedingly low," Reti adds. Even more important to patients is the lack of the cognitive side effects that can occur with electroconvulsive therapy, the other stimulation-based approach to depression. And unlike ECT, there's no need for anesthesia. "Aside from mild headache in some, patients don't have complaints," he says.

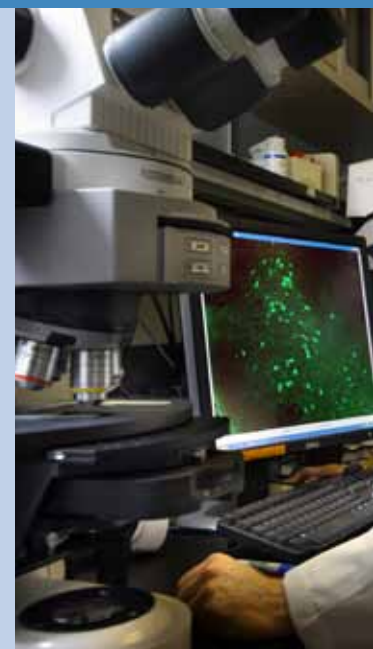
This could make TMS a good option for people who can't tolerate antidepressant medications or who, like transplant patients, are endangered by drug interactions. "We may also find out it's useful in pregnancy," Reti adds. The way is open, then, for clinical trials. As a start, the Hopkins group has two under way. One will study TMS in teens from 15 to 18 years old

with entrenched depression. The recent black-box warnings about antidepressants in this group, Reti says, spurs that trial on.

A second study—with adults—uses a variation of TMS that penetrates deeper brain. Because the technique's electromagnet is open to creative design, an experimental deep-brain version of TMS can reach beyond the 3 centimeters of prefrontal cortex that standard therapy touches. Exciting the deeper ventromedial prefrontal cortical pathways that control pleasure and motivation may make TMS more effective, Reti says.

He can't wait to start. ■

To call the Brain Stimulation Center: 410-955-5212. For research information: 410-614-1732.



# Opioid Maintenance: Make New Meds But Keep the Old

In spring 2006, a rare overcrowding struck The Johns Hopkins Hospital. It had barely a bed to spare—not a happy situation for a major medical center. Though many suspected why, it took a proper study to ferret out the real problem. And it was this: A substantial number of hospital patients surveyed reported substance abuse (SA) disorders, either adding to the illness that sent them to Hopkins or as the main reason they came. Arranging discharges for such patients well enough to go home was just short of nightmarish.

The SA situation wasn't a Hopkins specialty—it continues to flummox every U.S. city's medical centers. Part of the problem lies in numbers. In 2007, for example, Maryland hospitals admitted more than 69,000 patients for SA treatment. Nationwide, closer to 2 million filled hospital beds. And what the local and national figures reflect is a falling short in medicine's ability to see the big picture of substance abuse and to keep that picture current.

If the SA difficulty is something of a Venn diagram where neurobiological, social and political issues overlap in one murky triangle, we have to be willing to go into the thick of it, says addictions expert **Eric Strain**.

There are immediate steps to take, Strain says—electronic records, for example, should help streamline clinical services. But the broader perspective is getting more attention at Hopkins: A new Center for Substance Abuse opened this spring—under Strain's direction—to advance research and bridge treatment efforts on Hopkins' two medical campuses. The center is charged, in part, to fill gaps in patient care. But it's also bent on raising evidence-based treatment beyond a presently high level—the fruit of a half-century of Hopkins research.

"We want to create a research-based model of care for the



nation," says psychiatrist Strain. "But that means bringing an understanding of all the overlapping elements to the care of individual patients." It's tailoring to a new degree.

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For more than two decades, Strain has taught and researched addictions treatment. From expertise in pharmacology, he became well-versed in the behavioral, policy and economic issues as well as the epidemiology of opioid misuse. His recent book with colleague Maxine Stitzer, *The Treatment of Opioid Dependence*, was cited as "required reading that shaves years off a steep learning curve for new practitioners."

We've questioned Strain on one issue—maintenance treatment for opioid addiction—to get a feel for SA's "murky triangle." Compare older methadone replacement therapy with newer buprenorphine, we asked. Both help keep patients off heroin, for example, or prescription painkillers like oxycodone.

**Methadone clinics have stayed full since the 1960s. But Hopkins did many of the primary studies the FDA used in 2003 to approve buprenorphine. Why? Wasn't methadone enough?**

Buprenorphine and methadone have different pharmacologic profiles; it's not like, say, Zoloft and Prozac, which are closer. Having options is good. *There's a need for both*; we prescribe both at Hopkins. But buprenorphine's main advantages aren't so much pharmacologic as they are social.

**Explain.**

Historically, researchers readied buprenorphine to be available through a delivery system different from

methadone's. Methadone is very safe when used properly but it's highly regulated; you only get it through special clinics. In the past, some of those weren't well run. Communities saw that and didn't want new ones around—not in my neighborhood! Expanding the clinics became extremely difficult, though recently that seems to be changing as government oversight and treatment standards improve.

**And buprenorphine?**

Buprenorphine was developed for doctors to prescribe from their offices—to have physicians provide mainstream treatment for addictive disorders as part of their practices. We encourage that by offering buprenorphine courses here for professionals. The feeling is that it has a relatively low abuse potential. A high dose of methadone can be fatal in someone not physically dependent on opiates. Buprenorphine has less risk. Also, some patients report that it helps them feel more clear-headed. All of that simplifies things.

**What about the shift in drug abuse that caused such a swell?**

From the mid-1990s, we've seen a dramatic increase in misuse of prescription opioid painkillers. These users are less likely to be poor or homeless; they're often married and employed and don't abuse other substances like heroin. It's a good population for buprenorphine.

**Do people on buprenorphine stay with treatment longer than those on methadone?**

No. We studied retention; it's the same. All SA programs have substantial dropout. And no matter which program you're in, the longer you're in, the better the outcome.

**A last word?**

These are medical disorders we're discussing, and people suffer greatly with them. Simply punishing someone because of abuse is a narrow and inhumane approach. We use other ways to help, and they're a lot more effective. ■

## SUPPORTING THE CAUSE

### From Donor to Catalyst: Gruss Knows How to Help

**A**udrey Gruss didn't begin to make her mark on depression until she lost Hope. An international philanthropist, she and husband Martin have for years underwritten anything, really, that lifts the human spirit: supporting theater, music, art, offering scholarships, improving hospitals, preserving architecture. But it was the death of her mother, Hope, that galvanized Gruss's giving in a new way.

"Trauma early in my mother's life must have brought out her depression," says Gruss. Hope Butvydas, a sensitive, artistic woman, fled from post-war Communist Lithuania to America with two young children in tow. She fell ill. And for some 40 years, she was periodically hospitalized with a depressive illness that seared the meaning of suffering in her daughter's mind.

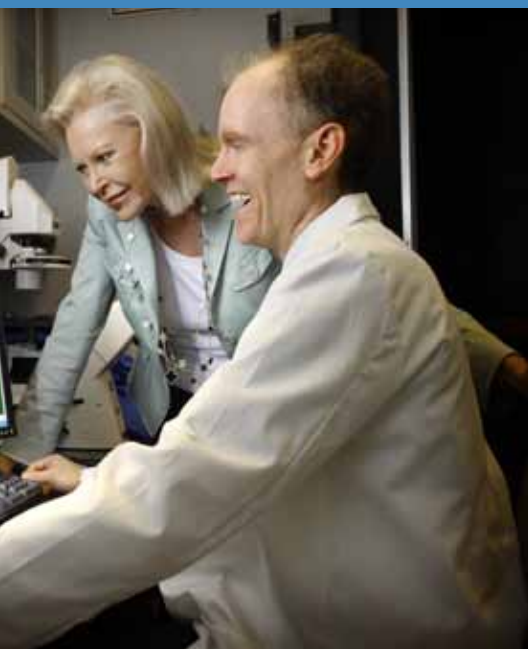
Gruss studied biology at Tufts University. A cum laude graduate, she worked for the research arm of Revlon, then, after studies in economics, began a 25-year career in marketing and advertising. She headed creative services worldwide for Elizabeth Arden and had her own successful international firm offering science-based skin care products. Her marriage flourished; her philanthropy grew.

But in 2005, when her mother died of medical causes, giving became more personal as a bereft Gruss searched for a memorial. And at one of those peak moments where interest, curiosity and experience overlap—as though Gruss had been in lifelong training for it—the way became clear. In 2006, after consulting some of the nation's best minds on mood and emotional disorders, she founded the Hope for Depression Research Founda-

tion (HDRF), an organization that underwrites targeted, gutsy studies with high potential to advance diagnosis, treatment and prevention of these mind-brain disorders.

By giving serious support to top international scientists—those whose work shows how neurobiology drives the psyche—the HDRF joins Hopkins in looking for both cure and prevention.

Irving Reti's HDRF grant enables him to help patients as it advances understanding (see story, left). With his supported work, Hopkins has become one of a handful of sites testing the next generation of TMS devices. HDRF is specifically funding a pilot study using TMS for adolescents—currently the only trial that focuses on this vulnerable group most in need of an alternative to antidepressants. ■



"It would be wonderful if TMS proves effective in adolescents—a breakthrough in ways to help them," says Audrey Gruss of Reti's upcoming study.

# When Ventilating Is Devastating

**N**ot long ago, success for people in the ICU with acute lung injury was easy to mark: It meant getting off the ventilator alive.

But as intensive care specialists began following patients once they left the ICU, they saw that too often, all wasn't well for these formerly sickest of the sick. That prompted a rush to fine-tune ventilator use, and things improved: Simply cutting back air pressure, for example, helped lower a 70 percent risk of death to 40 percent.

Yet some patients—perhaps a third—haven't snapped back to health weeks or months later. For them, lungs can heal in six months, but not so the mind. That's of some concern to psychiatrist **Joe Bienvenu**. A specialist in anxiety disorders, he was recently asked to cover psychiatric parts of a new Hopkins study of post-ICU patients. The study—Improving Care of Acute Lung Injury Patients—follows the formerly “ventilated” from 11 Baltimore hospital intensive care units up to five years later.

Bienvenu was turned around by what he read and saw.

“I was hesitant at first to sign on,” he says. “When I heard that these patients suffered from PTSD, it seemed kind of far-fetched.” So he and Hopkins colleagues began by confirming the problem; they reviewed data from earlier, smaller studies of intensive care survivors. PTSD clearly looked genuine.

Yet it was seeing patients that most affected Bienvenu. “It only took a few and I was convinced,” he says.

Consider John Lyons,\* an amiable, soft-spoken man whom Bienvenu invited to a departmental grand rounds. Lyons, a self-described perfectionist in his 40s, comes from “a family of worriers” and lives with his father. He was once treated



for depression. But two years ago in the ICU, Lyons' amiability disappeared. Viral pneumonia had made him septic. Suffering acute respiratory distress syndrome, he was sedated and intubated for a month to save his life. He became delirious.

In his delirium, Lyons was convinced he was being tortured in death's basement where the walls dripped both blood and flesh—a common hallucination, it seems. Severely agitated, he punched nurses, requiring heavier sedation and restraint.

Once home, the newly frail man tried to be positive, but flashbacks and insomnia troubled him months before he sought help. With medication, his PTSD lifted, though he's still uneasy at times.

“It's no surprise that many patients

suffer after-effects,” Bienvenu says: They've been acutely ill. Their shortness of breath alone is frightening. Their widespread inflammation surely includes the brain. They're restrained. Intubation is painful, and many of the drugs they need—benzodiazepines and catecholamines—stress the psyche at high doses.

Bienvenu's review brought out risk factors for PTSD that bear more investigating. Having a history of anxiety or depression is one. So is having intense memories. “For many patients,” says Bienvenu, “these experiences are oddly more real than daily experiences. And they last—they're memories of fighting for your life.”

Medication is also suspect. The very benzodiazepines that ease breathing and damp down patients' primal anxiety at being intubated are tied to both delirium in hospital and to PTSD

once they're out.

Now the task, says Bienvenu, is to get a coherent picture and see where changes could be made. One working hypothesis is that patients who're sensitive by nature become more agitated in the ICU and need more medication. They suffer more potent hallucinations, perhaps, which, in turn trips anxiety attacks once they're home. Only more work will tell. The five-year study should help, if only to confirm a need for ICU alternatives. Already, there's a suggestion that administering steroids to damp down inflammation may shield the brain from severe effects.

Meanwhile, Bienvenu says, “just knowing who we should and shouldn't worry about in the ICU could make a difference.” He is especially interested

in what role temperament plays, how it might predict who needs more reassurance and watching. “It could be,” he says, “that intervening early goes a long way.”

For information: 410-614-9063

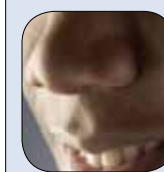
\*To protect privacy, we've changed the name and details.

## Coming this Fall

Look out for our special all-research issue of *BrainWise*—a quick primer on just-off-the-bench studies or just-out-of-clinical-trials results. We're spanning the fields of Hopkins psychiatric science, from schizophrenia to Alzheimer's, child psychiatry to substance abuse to depression.

And we're sure to include this news:

■ Schizophrenia's cause is likely both genetic and environmental, but the overlap is really hard to tease apart. Exposing animal models of schizophrenia, in utero, to the effects of common viruses may do the trick.



■ The greatest advances in schizophrenia research may come from...the human nose. New studies of CNS stem cells plucked from patients' olfactory tissue may

lead to a high degree of tailored therapy for the disease.

■ How to stop anxiety disorders? Catch them early on, in the bosom of your family before they start.



■ An antidepressant that lifts mood in substance-dependent women may also help them stop smoking.

## Hopkins *BrainWise*

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