

TRANSLATIONS

Tots with ADHD: It's OK to Treat

With a new spate of studies just out, the picture of ADHD and its most common medicine has come into focus for the children now under scrutiny—those age 3 to 5.

It's the latest work from the nationwide, government-funded effort—the Preschoolers with ADHD Treatment Study (PATS)—which, because of the tender age of its subjects, has been nearly a decade in the doing.

The research, which involves Hopkins child psychiatrists, shows that stimulant (methylphenidate) therapy works and that lower doses can be used in this youngest group with attention deficit hyperactivity disorder.

"Elementary-school youngsters with ADHD are comparatively well studied," says child psychiatrist **Mark Riddle**, an author on all of the new journal reports.

"But we lacked much of anything concrete for their younger brothers and sisters." And because Hopkins, like the rest of the country, is seeing more and more preschoolers with ADHD, the need for good treatment data is urgent. Gathering data in younger children also makes sense on a more basic level, since that's typically the disorder's onset time.

"ADHD is a huge public health issue," says Riddle, one of the study's planners and head of the Hopkins branch. One of the most common psychiatric disorders in children, it affects up



Putting together a major study of children only slightly older than toddlers—it screened almost 2,000 of them—put feasibility and ethics face-to-face. Mark Riddle, however, pushed on. The results, he says, compensate for a decade of effort.

to 8 percent of them in this country. That's more than 4.5 million, he adds, with some 250,000 youngsters "minted" each year.

The first PATS results—appearing in 2006—showed that preschool ADHD is in some ways unique. For one thing, the youngsters need comparatively less methylphenidate. Tiny 1-milligram pills three times a day became the best dose for nearly a quarter of the children with uncomplicated ADHD, once

side effects were factored in. Those effects were more frequent in the preschoolers and could take a slightly different tone, Riddle says, with labile, hair-trigger emotions, for example, or some children seeming "a little blunted" in a way the older ones didn't.

As for this year's results, the best is finding that methylphenidate works; it's effective even through a 10-month maintenance period. Overall, children continue to act better and fit in better

socially. That's encouraging, Riddle says, because ADHD symptoms were more severe in the PATS preschoolers, the newest data show. Almost 70 percent have additional problems with behavior or communication, for example. The largest concern is slowed growth. Though not all children on the stimulant experience that, the effect is generally greater in the younger ones, averaging a yearly half-inch lag in height and three pounds in weight from norms. "If ADHD were episodic, more like depression, that would be less of an issue. But the disorder sticks around," says Riddle, and treatment is often long term. "Parents now have to consider if it matters that children are 5'11" instead of 6 feet tall," he adds.

Each wave of research leaves questions in its wake. Can something be done to whittle down growth loss? Would side-by-side psychosocial programs ease the need for prescriptions? Hopkins has been exploring that. PATS began, for example, with 10-week training for parents in behavior management—tactics they could use in the home to lessen problem behavior. "The parents loved it," says Riddle, but only 7 percent of the children saw their ADHD improve. "Still, that pushes us to look for alternate therapy, if only to let us use less medicine." ■

For information, call 410-955-3246.

Untying ADHD's Diagnostic Knots

Maddie Tate* is 12, bright and kind. Her mother calls her Maddie-in-Space, however, because she leaves textbooks at school and her bedroom is a temple to unfinished projects. A pile of otherwise-empty notebooks, each with a snatch of a poem, gathers dust. The girl who came to Hopkins' new ADHD and Behavior Disorders Program was distant after a row with her parents over a D in algebra.

"To us, children like Maddie aren't unusual," says child psychiatrist **Justine Larson**. And treating them highlights the program's strength in untying diagnostic knots. "People often think that children with counter-productive behaviors have a single problem," she explains, "but we usually see otherwise. Our job is to parse the behaviors and find their causes."

Maddie's pediatrician suspected inattentive ADHD, a less common form more common in girls. "It's a real problem in learning and staying tuned in," says colleague Mark Riddle. Larson had that in mind during an initial several-hour interview with the girl and her parents. She took psychiatric, medical and social histories, including a screening for anxiety and depression. Maddie, her parents and her teachers also completed a behavior assessment. Program psychologist **Rick Ostrander** administered neuropsychological tests for learning disabilities, executive function and IQ.

"We collect a lot of collateral information," Larson says. And Maddie, it was found, probably does not have ADHD, though she'll be observed at follow-up visits. She does, however, have a learning disability that makes summarizing reading painful, partnered with an anxiety problem made acute by the prospect of high school and worries about grades. She scored high on a depression inventory.

What to do? Larson has prescribed anti-anxiety medication for Maddie and placed her in a cognitive behavioral therapy program that's already improving her mood. Her parents are learning elements of behavioral management to add structure at home and avoid disharmony. Other tactics sidestep her learning problem, though her focus is improving as her depression eases. ■

* Maddie is a composite of patients.

For information, call 410-955-1925.

A Suicide Gene

Studies suggest it's a thing apart.

PAGE 2



The Glass Half-Empty

Personality apparently makes a difference in anxiety disorders.

PAGE 3

Zero-to-Five

New Help for Our Most Vulnerable Patients.

PAGE 4





“Our next studies to see if statins could change things are under way,” says Mielke.

Alzheimer’s: Circulatory Ills Give It a Push

Could fixing them make the disease less relentless?

Angina. High blood pressure. Heart arrhythmia. A number of studies have singled out flaws in the circulatory system, or combined them even, to see if they raise a person’s likelihood of Alzheimer disease (AD). The most telling ones, the long-term projects that follow large swaths of the adult population, make it clear: So-called vascular factors do increase the risk of the dementing illness.

But what about those who already have the disease? “Once Alzheimer symptoms appear, we haven’t seen much interest, so far, in looking at the effects of vascular problems,” says epidemiologist **Michelle Mielke, Ph.D.**, a researcher in geriatric psychiatry.

That may change, however. Until a cure arrives or AD can be prevented, a focus from within the disease could put some benefits in easy reach. New work by Mielke and her Hopkins colleagues, reported in the November issue of *Neurology*, first suggests that patients with key signs of circulatory disease undergo a faster

Alzheimer-caused decline. But it also leaves open the possibility—one needing study—that improving circulation might slow it.

Mielke’s team analyzed data from 135 men and women over 65, all newly diagnosed with AD. Most of the group was followed for three years and rated every half year on cognitive abilities including memory and on how well they carried out everyday tasks. A physical exam at the time of their diagnosis gave data on circulatory health, with such touchstones as high blood pressure (and having therapy for it), history of the abnormal heart rhythm, atrial fibrillation, heart attack history, diabetes, smoking or angina.

The research is strong, Mielke says, partly because the patients were part of a much-respected and still ongoing study of aging and memory that began in Cache County, Utah, in 1995. That project enrolled more than 5,000 elders, and the expertise of those testing them has made the data extra trustworthy.

“But the fact that it’s a popula-

tion study is also a strength,” says Mielke. “We’ve watched these participants more than a decade, even before their AD diagnosis, so we know a good deal about their medical history and onset of the disease.” It’s not the same, she adds, as picking already ill patients from a clinic to study them.

In the end, the bad-news trio of dangerous arrhythmia, hypertension or angina are especially obvious in their tie to Alzheimer’s progress. In a group with high blood pressure, for example, rate of memory loss roughly doubled. And though not quite that quick in those with atrial fibrillation, memory decline was still significantly faster.

Could improving circulation slow the disease? “That’s what we’re looking at now,” says Mielke. She’s with a Hopkins team looking at effects of existing drugs that lower blood pressure, among other things. “We’re optimistic that there’s something to it.” ■

For information: 443-326-5174

Closing In on a Suicide Gene

The newer tactics to find genes for psychiatric illnesses seem a bit like sitting at a microscope and flipping to a higher power lens. The searches are finer, more tailored. And like narrowing a ‘scope’s field, they focus on “pure” groups in the population, a move that may force a desired gene or genes into the open.

So this decade has had depression research, for example, that looks only at those who’ve suffered from an early onset of the illness, or a search for bipolar disorder (BP) genes that picks out people with psychosis as a symptom. Recently, the new mindset has brought us closer to confirming a genetic hand in suicide.

This year, a study by a Hopkins team and other collaborators linked a specific area of chromosome 2—section 2p11-12—to attempted suicide. What makes that exciting, says geneticist **Virginia Willour, Ph.D.**, is that two earlier studies implicated the same site. “We’re all in the same place,” she told an online reporter. “And that’s pretty unusual. Sometimes you may

be in the same ballpark, but these were right on top of each other. This is fantastic for those of us interested in finding genetic risk factors.”

The concurrence, along with the fact that the research was on patients with different psychiatric illnesses, suggests something important about suicidal behavior, that it’s in some ways independent of the usually accompanying disease. This fits in with the so-called *two-hit* idea that says people most likely to attempt suicide have both a psychiatric illness like BP, major depression or alcoholism and a second, independent risk factor. Possibly, that factor is what the studies are flushing out.

Willour’s team pulled data from an existing, whole-genome analysis of 162 families with bipolar disorder. They focused on differences in members of that group with positive answers to survey items about attempting suicide. One of the two earlier studies took a similar approach but looked at suicide attempters in families with major depression. The other focused on those in

families with alcoholism.

And the nature of the independent factor, once it’s found? The geneticists suggest it may be tied to an increase in “impulsive aggression.”

Also, because a number of physiological studies suggest that suicide attempters are low in serotonin, it’s tempting to think that genes in that neurotransmitter’s pathways are involved. Willour cautions, however, about jumping the gun. “Just because we think a gene should be related to suicide doesn’t mean the body does.” Only finding the gene on chromosome 2 and tracing its function will tell.

That would be the next step.

Now Willour is pressing on to a far larger study—ultimately some 4,000 patient and control DNA samples. It could be powerful enough to pull the gene from an increasingly narrow field of candidates.

“Our goal,” she says, “is to identify patients at risk of attempting suicide. We also want treatments—medications—with a rationale based on the biology.” ■



“Side effects of medications can overwhelm some patients,” says Willour. “Genetics is one way to get better options.”

Anxiety and Personality: Strangers No More

Humanity is in some ways like a deck of cards. And most clinicians, confronted with the hand they're dealt from day to day, find that people fall into fairly standard suits, personality-wise. The idea of stable personality traits has been with us at least a century. Though questions of which categories are truest and how they form have sparked heated discussion ever since Freud and his social psychologist contemporary George Herbert Mead first wrestled with them, the thought that personality has some bearing on psychiatric illness has never been doubted.

It's just been understudied.

Joseph Bienvenu, M.D., Ph.D., wants that to change. Clinically, Bienvenu, a psychiatrist, diagnoses and treats anxiety disorders. His training as an epidemiologist, however, equips him to tease out parts that personality traits play in the "distress disorders" of anxiety and major depression. Bienvenu's focus is on two traits: neuroticism—the tendency to experience negative emotion and cope poorly with stress—and being introverted or not.

His early work shed light on the basics, namely, showing that personality traits and problems like agoraphobia and panic disorder are somehow tied. Data for these first studies came from offshoots of the Baltimore Epidemiologic Catchment Area survey, which Uncle Sam commissioned in the 1980s to paint the first real picture of mental illness in this country.

Bienvenu's more recent work goes a step further. It suggests that traits like high neuroticism and introversion signal an underlying genetic risk for anxiety disorders.

If a person is high in neuroticism, does that sort of personality bring on the phobias, the panic attacks?

Historically, there was that thought. But saying one causes the other is simplistic, I think. More likely, it's that vulnerable personalities *predict* the disorders. Studies with twins are helpful here. We know—from comparing identical and fraternal twins—that personality traits have a genetic basis. But we're also finding that the very genes that make someone prone to high neuroticism are the same ones to raise the risk, say, of generalized anxiety disorder. And it's not just the one personality type. Our recent work suggests that genes underlying introversion also increase the chance of having social phobia or agoraphobia.

That screams "common biology."

Yes, and it may be broader than we've thought. There's an idea of a spectrum of genes that relates personality traits and most of the distress disorders. High neuroticism, for example, is common to so many of them—depression, social phobia, panic and generalized anxiety disorder. If we could hit on the biology behind neuroticism, wouldn't that be a home run for understanding the distress disorders?

So can you use personality tests as predictors?

It looks that way. My Hopkins colleague Jim Fauerbach, for example,



sampled personality in Hopkins burn unit patients. High neuroticism and introversion predicted the onset of PTSD within a year. And elsewhere, with UN peacekeepers in Europe, the findings were similar.

They should use that in Iraq!

It'd make a lot of sense for the military to measure neuroticism, not to exclude new recruits but to know who's at high risk based on temperament.

Can personality change?

Yes. It appears "fixed" by age 35, *but* psychiatric disorders can bring on at least temporary change—we've known

that for years in the context of depression. Then patients get a kind of a bias and selectively remember negative things. And for patients acutely ill with panic disorder, everything looks much scarier; they feel more vulnerable. Brain function itself may change, then go back toward baseline when they're better.

Completely?

Almost, we think. The scars are small.

Could you change personality, do you think, to head off disorders?

Yes! One Australian study on young children at high risk showed that psychotherapy could do just that. We need more data though. Preventing anxiety disorders is very much on our minds. And because many of them tend to begin in young people, we're looking at children and teens—more twin studies—first in baseline work to see how well high neuroticism predicts later disorders in young adults. This sort of research could be a basis for prevention.

I'm feeling sorry for the neurotic and introverted of this world.

Don't. They have their strengths! People high in neuroticism are sensitive and tend to stay out of certain kinds of trouble—like accidents. And introverts really stick to projects without jabbering with others. Without them, this country would come to a halt. ■

PHIPPS FACTS

The MMSE Earns Top Title

In 1973, after making her rounds of geriatric patients at Cornell Medical Center's Westchester Hospital, resident **Susan Folstein** would report on their mental state to husband **Marshal Folstein**, who happened to be attending psychiatrist. "She'd tell me, 'Mrs. Jones is doing better today, or she's doing worse,'" says Marshal. "But I'd always reply, 'How do you know that?'"

Hopkins' well-known psychiatrist **Paul McHugh**, now University Distinguished Service Professor, was then the residency training director at Cornell. "Because Susan was married to Marshal," McHugh jokes, "she could only put up with this so long." Finally, an exasperated Susan asked one day, "Why don't you just write down the questions you want me to ask?" So that night Marshal did.

His previous neurology training prompted questions that were simple, direct, objective—*What day is it? Count backward from 100 to seven*—but they were also extraordinarily telling. They measured orientation, comprehension, recall, reading, writing, drawing (visuospatial) tasks. He called the final 11-question

product the Mini Mental State Examination (MMSE). Patients could take it in 10 minutes.

Ultimately, the Folsteins set up a trial of the MMSE with 206 patients to see if it could distinguish various cognitive disorders. It could. Scores reliably teased out dementia or depression from normal cognitive function. "We were just kids; we didn't have any training," recalls Marshal. They just wanted something to improve their work. But the test was revolutionary. "It became obvious," says McHugh, "that nobody else had anything like it." With his help, the pair submitted their study to the *Journal of Psychiatric Research*; it was published in 1975.

The rest is history. Once at Hopkins, the Folsteins and their colleagues put the MMSE to work in definitive epidemiological studies on the scope of mental illness, for a starter. Now it's been translated into more than 35 languages. Referenced in almost 20,000 journal articles, the MMSE is the most cited paper in neuroscience and geriatrics and, as noted in a recent psychiatric journal letter, probably the most frequently cited ever in medicine. ■



For Babes in No-Joy Land

Why a new, whole-family approach can make a difference for the smallest patients.

Lice, stomach flu and a swirl of family chaos. **Joyce Harrison's** recent description of what's routine drove home the scope of programs she heads for children age 0 to 5.

Harrison, one of only a small number of psychiatrists to specialize in that age group, oversees a new diagnostic clinic at the Hopkins Bayview campus and an even newer outpatient program—both often a last resort in reversing toddlers' downhill trajectories. She described both in a recent Psychiatry seminar.

"We'd always assumed problems started at age 6, when troubled children appeared at school," says Harrison. "But I'm seeing them much younger." Of the young ones at the preschool clinic since its March opening, more than a third were age 3; two patients came at a year old. "Problems in this age group had been written off as bad behavior or poor parenting. Yes, the causes can be environmental. But, in many children, biology's clearly at fault."

Take Amy, born prematurely to a mother on cocaine.* She came to the clinic at age 3 because of violent behavior toward siblings and an unhealthy fecal fascination. Amy has low muscle tone; she's clumsy and speech-delayed. Her

father suffers from anxiety disorders. Under stress from their own problems and the imbalance Amy brings, the parents argue frequently. The only time there's calm, the mother explains, is well after midnight.

"Kids come to us because of behavior problems," says Harrison. They're aggressive, hyperactive; they can't go out in public—the presentation is almost a stereotype. So Harrison must resort to detective work. "Everything is by inference in this age group," she says. "You have to watch, interpret." The Infant and Toddler Mental Status Exam and developmental screens she and her team employ involve rating play behavior, for example, or reactions to new situations. She routinely videotapes children in the programs' playroom.

What underlies Amy's behavior, roughly put, is wiring. She was born with a chemical exposure. Yet family problems all contribute. How, then, do you help this new person whose needs are so pressing?

Harrison realized early on that weekly therapeutic visits would change little. Also, sending children out for wait-listed speech and other evaluations means unacceptable delays. So she and Hopkins colleagues set up the Preschool Therapeutic

Learning Center (PTLC), an intensive program that, unlike others, enfold a child's core family, three hours a day, five days a week. "About 90 percent of our parents have a psychopathology," she explains, "and the siblings aren't without problems."

But whether diagnosing or treating, the team sees obstacles in the lack of valid diagnostic categories for preschoolers and the slim number of evidence-based treatment protocols (an exception: PATS, page 1). "There's little precedent for what we do," says Harrison. So their mainstay is considerable collective experience.

Harrison has ties to a trusted network: clinician-pioneers in early child psychiatry, Head Start experts, Maryland's Early Childhood Mental Health Steering Committee, a study group for the American Academy of Child and Adolescent Psychiatry, and academics at the University of Maryland who've run a 20-year infant study program. "It's taking a village to do right by these children," Harrison says.

So a taxi was sent for Amy's mother, father, baby brother and 5-year-old sister to bring them to the PTLC's airy, sunlit playroom high in the west Mason Lord tower. It's a low-stress environment, much like a preschool but



more structured and more supervised. While Amy and her sister were in play (therapy) groups or seen singly by a therapist, their parents were registered for psychiatric or addiction services.

The first weeks were rocky. Often, one parent didn't come. The baby was sick. Harrison's discovery that Amy had lice got the family packed off in a taxi to the pharmacy and then home. Stomach flu kept them away for days. On their return, lice were rediscovered; the older sister threw up: It was back to the pharmacy in the taxi. With each day, however, the family became more resilient. "You could watch the parents' attitude change," says Harrison. "They see us all working to help their children and say, *Wow, my child really has value*. They realize problems can have a solution." On Fridays, she says, the families don't want to leave. ■

For information, call 410-550-0104.

*For privacy, Amy's story is changed in kind but not spirit.

The Bubble Test and More

We asked early childhood psychiatrist Joyce Harrison some specifics.

What are your feelings on medications for the 0-to-5s?

They're absolutely a last resort. Less than 2 percent of our patients use them and then, only the few medications clinicians are comfortable with, like some stimulants and SSRIs. I'd rarely use the antipsychotic Risperdal (just approved for this group) and, then more for sedation and cognitive organization. Given preschoolers' amount of imaginative and fantasy thought, it's both difficult and rare to see psychosis!

What about bipolar disorder or depression?

I have an extremely high threshold for calling anything bipolar. I think it's much overused in the young. That doesn't mean it doesn't exist. At this age, it's characterized by grandiosity beyond what's age-appropriate, sometimes hypersexuality and hyperactivity. You look for family history.

The main signs of depression in this age are withdrawal, a lack of pleasure. I find the bubble test helpful. Most kids are joyful around bubbles. If they don't respond, they're often depressed. They also withdraw, are a little irritable. ■

BrainWise

This issue of *BrainWise* is published by Johns Hopkins Medicine Marketing and Communications for the Department of Psychiatry and Behavioral Sciences.

It is distributed to the scientific community, sponsors, friends and others interested in the department's research and activities.

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

© The Johns Hopkins University 2007

To make a gift to the Department of Psychiatry and Behavioral Sciences, contact Jessica Lunken, Director of Development, Department of Psychiatry, 100 North Charles Street, Suite 410, Baltimore, MD 21201, 410-516-6251

If you no longer wish to receive this newsletter, please e-mail mcintoshanti@jhmi.edu

Save the date! The 22nd Annual Mood Disorders Research/Education Symposium features skater Dorothy Hamill and TV actress Mariette Hartley.

Tuesday, April 15, 1-6 p.m. at Hopkins' Turner Auditorium

For information, call 443-287-3480.

J. Raymond DePaulo, M.D., Chief of Psychiatry

Patrick Gilbert, Director of Editorial Services

Marjorie Centofanti, Editor/Writer

Virginia Hughes, Writer

Dalal Haldeman, Vice President, Marketing and Communications

David Dilworth, Designer

Keith Weller, Photography

Editorial Office
901 South Bond Street, Suite 550
Baltimore, MD 21231



Non-Profit Org.
U.S. Postage
PAID
Permit No. 5415
Baltimore, MD