SSRIs make common opioids less effective

By Mandy Erickson

Patients taking the most common form of antidepressant who are given the most widely prescribed opioid experience less pain relief, School of Medicine investigators have discovered.

The finding could help combat the opioid epidemic, as poorly managed pain may lead to opioid abuse.

As many as 1 in 6 Americans takes antidepressants, mostly selective serotonin reuptake inhibitors. Stanford researchers found that SSRIs reduce the effectiveness of hydrocodone and codeine, which are often prescribed to patients who have recently undergone surgery.

“This research is part of our effort to find ways to combat the opioid epidemic,” said Tina Hernandez-Boussard, PhD, MPH, associate professor of medicine, of biomedical data science and of surgery at Stanford. “We’re very interested in identifying how we can reduce opioid exposure while still managing patients’ pain.”

A paper describing the research was published Feb. 6 in PLOS ONE. Hernandez-Boussard and Ian Carroll, MD, assistant professor of anesthesiology, perioperative and pain medicine at Stanford, share senior authorship. The lead author is graduate student Arjun Parthipan.

Antidepressant inhibits enzyme

The researchers focused on the interaction between opioids and SSRIs because they knew that certain opioids, called prodrug opioids, need a liver enzyme to convert them into an active form that eases pain.

SSRIs inhibit this enzyme, so the researchers hypothesized that patients taking SSRIs in combination with prodrug opioids would receive less pain relief. Prodrug opioids include codeine and hydrocodone, which is sold under brand names such as Vicodin, Lorcet and Lortab. SSRIs include Prozac, Paxil, Zoloft and Celexa.

For the study, the research team analyzed de-identified data for 4,306 surgical patients with a diagnosis or symptoms of depression in the electronic health records at Stanford Health Care.

The researchers found that the patients on SSRIs who were prescribed prodrug opioids experienced more pain when they left the hospital, as well as three weeks later and eight weeks later. The patients on both SSRIs and prodrug opioids registered nearly one point more pain on a scale of 1 to 10 than the patients not on SSRIs who were prescribed prodrug opioids.

Algorithm predicts opioid response

The researchers built a machine-learning algorithm that predicts how a patient will respond to different types of opioids. The algorithm is available online at https://doi.org/10.25936/kjx8-0w74.

The study focused on surgery patients because they nearly always receive opioid prescriptions, yet the information supply to anyone taking short-term opioids.

Carroll noted that hydrocodone is the most frequently prescribed drug in the nation. With SSRIs the most frequently prescribed class of drugs, he said, the chance that any patient will be on both drugs is high.

There’s no proof that better pain management reduces the number of opioid overdoses, cautioned Carroll. But poor pain control has been shown to be a risk factor for chronic pain, and it may lead to more prolonged opioid use, along with misuse.

“Presumably, every day you take opioids, the risk you’ll abuse it increases,” Carroll said.

The authors concluded that to manage pain for patients on SSRIs, prescribers should choose nonopioids or direct-acting opioids. Direct-acting opioids, which include morphine, fentanyl and oxycodone, do not need the liver enzyme to convert the drug into a form that eases pain.

Prescribers typically choose hydrocodone or codeine because of a perception that they are

Male mice are hard-wired to recognize sex of other mice, according to new study

By Bruce Goldman

A male mouse identifies the sex of an unfamiliar mouse because of hard-wired brain physiology, not previous experience, School of Medicine investigators have found.

The researchers identified, for the first time in mammals, a small number of neurons in the male mouse brain driving a sexually inexperienced animal’s ability to speedily determine another mouse’s sex.

Female mice also quickly determine a stranger’s sexual identity. But the circuitry in their brains that guides those decisions remains to be located.

“Surprisingly, recognition of a stranger’s sexual identity works completely differently in male and female mice,” said Nirao Shah, PhD, professor of psychiatry and behavioral sciences and of neurobiology.

The findings, described in a study published Jan. 31 in Cell, add to a small but growing list of mammalian brain circuits known to work differently in males and females. They inform a long-standing debate about the relative contributions of inherently hard-wired predispositions versus socially acquired influences in molding sex-specific behaviors.

Shah is the study’s senior author. The lead author is postdoctoral scholar Daniel Bayless, PhD.

Researchers identified neurons that enable male mice to quickly identify the sex of unfamiliar mice. The finding may apply to humans because the two species share much of the same brain circuitry.

Set of genes can predict severity of dengue fever, according to new study

By Hanae Armitage

There’s no such thing as a “good” case of dengue fever, but some are worse than others, and it’s difficult to determine which patients will make a smooth recovery before they leave the hospital, as well as three weeks later and eight weeks later. The patients on both SSRIs and prodrug opioids registered nearly one point more pain on a scale of 1 to 10 than the patients not on SSRIs who were prescribed prodrug opioids.

SSRIs inhibit this enzyme, so the researchers hypothesized that patients taking SSRIs in combination with prodrug opioids would receive less pain relief. Prodrug opioids include codeine and hydrocodone, which is sold under brand names such as Vicodin, Lorcet and Lortab. SSRIs include Prozac, Paxil, Zoloft and Celexa.

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Prescribers typically choose hydrocodone or codeine because of a perception that they are
Rheumatoid arthritis is one of the most common autoimmune diseases, affecting about 1 percent of the population. It involves destruction of synovia, soft tissue that lubricates joints to prevent bones from scraping together. Whereas osteoarthritis is attributable to age-related wear and tear, rheumatoid arthritis results from a chronic attack on the synovia by cells of the body's immune system. The inflammatory character of rheumatoid arthritis also causes systemic problems. For example, the inflammatory character of rheumatoid arthritis in mice engrafted with human tissues, takes up residence there because they're full of cellular debris in the act of相关内容

Cornelia Weyand is the senior author of a study that found that shutting down a faulty molecular mechanism in “humanized” mice curbed the damage caused by rheumatoid arthritis in the animals.

Endnotes

1. Rhoads, N., and S. H. Yang. 2017. Rheumatoid arthritis helper T cells lack a regulatory molecule that senses ratios of glucose and ATP and its two main breakdown products. If it finds AMPK to become activated even when it's just floating around, it will shut down ATP production. The aberrant enzymes that are not the right size for our pediatric technologies, said Paul Goldman, MD, professor of immunology and rheumatology at Stanford Health Care’s Valley Post-doctoral scholars Ke Jin, PhD, Yi Shen, PhD, Yin Yin Li, PhD, and Bowen Wu, PhD; research associate Zhen Yang, PhD; Lu Tian, MD, associate professor of bio-medical data science; and Jing Gorony, MD, PhD, professor of immunology and rheumatology. The work was funded by the National Institutes of Health. Stanford’s Department of Medicine also supported the work. 

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Susan Ipakchian Director of print & web communications

John Sanford

Robin Weiss Graphic designer

Inside Stanford Medicine is an award of $6.7 million from the FDA. In addition, they found that a novel drug, which is not yet commercially available, helped protect both humans with the disease.

By Erin Digitale

Each year, far fewer medical devices are approved by the Food and Drug Administration for children than adults. This means pediatricians don’t always have top-notch tools available to address medical challenges in babies and kids. Now, a team of scientists and physicians at two of the Bay Area’s leading research institutions are collaborating to address the problem. Researchers at the UCSF-Stanford Pediatric Device Consortium, established last year with an award of $6.7 million from the FDA. "When you look historically at the approvals of devices that have specific pediatric indications, they're abysmal — essentially flat-lined," said James Wall, MD, assistant professor of surgery, who leads the Stanford side of the collaboration. The Bay Area group is one of five consortia receiving FDA funding across the country to try to bolster development of pediatric devices. The dearth of pediatric medical devices creates two challenges, Wall said. "We often end up having to cobble together adult-sized devices arounds to use adult-sized devices that are not the right size for our patients," he said. "There are also pediat-

Consortium fosters innovation in pediatric medical devices

School of Medicine investigators succeeded in countering inflammation and tissue damage caused by rheumatoid arthritis in mice engrafted with human joint-lining tissue and a human immune system. The inflammatory character of rheumatoid arthritis in mice engrafted with human tissues, takes up residence there because they're full of cellular debris in the act of...
Gardner on meat, protein and the environment

Vegetarians may be on to something: It’s entirely possible to get the National Academy of Medicine’s recommended amount of protein without eating meat. Per capita, Americans consume the most protein in the world and eat the most meat, according to a report published in Nutrition Reviews. The article, a literature review, analyzes recent protein consumption nationwide. Yet gorging oneself on protein doesn’t yield health benefits. In fact, excess calories — in the form of protein or anything else — can result in obesity and can lead to weight gain. So what’s more, studies have shown that raising enough livestock to satiate American meat consumption contributes substantially to carbon emissions and requires trillions of gallons of water.

One of the authors of the report, Christopher Gardner, PhD, professor of medicine at Stanford and the Rehnborg Farquhar Professor, and his co-authors recommend steps that individuals can take to curb carbon emissions and reduce the resources required to raise livestock, as well as improve the health of the planet.

In a conversation with science writer Hanan Anitram, Gardner discussed the problems with current protein consumption and how much individuals should be eating, as well as how the thinks the two can be reconciled in a way that will benefit the environment.

Christopher Gardner

Cattle in Hereford, Texas, known as the “Beef Capital of the World,” raising enough livestock to satiate American meat consumption contributes substantially to carbon emissions.

Do you recommend a cutback in meat consumption? How would that help reduce the impact on natural resources?

GARDNER: Given that many, if not most, Americans eat twice the amount of protein they require, there is a substantial room to consume less protein and still meet individual needs. Most people could choose a vegetarian or even a vegan diet and still meet their protein needs — but I am not necessarily pro- or anti-vegetarian. I would recommend two things: eating less protein in general and shifting the source of some protein from animal to plant foods. Keep in mind that, beyond protein, this shift to a more plant-based diet is now consistent with the recommendations of every public health organization regarding improving human health. In our paper, we modeled the impact of individuals consuming 25 percent less protein, and also shifting 25 percent of the remaining protein that they consume from animal to plant foods. For Americans, that would mean still getting most of their protein from animal foods, about a 60-40 split. By our estimates, that 25 percent-less-and-25-percent-shift recommendation would result in 40 percent lower carbon dioxide emissions from food production-related sources, which would be equivalent to about 8 percent of the greenhouse gas emissions reductions originally pledged by the United States under the Paris Climate Agreement. The shift would also equate to a 10 percent decrease in methane emissions and a 25 percent decrease in water consumption contributions.

What’s the connection between meat consumption, greenhouse gas emissions and water use?

GARDNER: Over the last decade, concerns about greenhouse gases and water usage have grown as the United States entered a period of urgency and emergency. There are now dozens of published analyses demonstrating that current agriculture practices are contributing substantially to accelerating global warming, and changes in agricultural practices will be essential to addressing climate change. This is particularly true of raising livestock, beef and dairy in particular, which is far more negatively impactful on resources than growing plant foods, which is relatively less resource-intensive and produces less greenhouse gas.

How would introducing a meatless diet in the United States affect the environment?

GARDNER: The data we cite from the Food and Agriculture Organization encompasses meat intake in more than 150 countries, and concludes that more meat per person is consumed in the United States than in any other country. The United States government’s guidelines have a “recommended daily allowance” that amounts to 0.36 grams of protein per pound of body weight per day. That equals 45 grams of protein for someone weighing 125 pounds, and 65 grams for someone weighing 175 pounds. But what’s important to note is that this estimation already has a built-in buffer to account for variability across the population. The majority of people should interpret the recommended allowance as a guide, not as a minimum requirement. If the entire population consumed the recommended daily allowance of protein, 97.5 percent would meet or exceed their requirement. And the average woman in the United States eats about 80 grams per day, and the average man about 100 grams per day. And that’s before adding protein bars, protein shakes and protein powders.

How can we help ensure a meatless diet is not only environmentally friendly but also healthy and affordable?

GARDNER: Given that many, if not most, Americans eat twice the amount of protein they require, there is a substantial room to consume less protein and still meet individual needs. Most people could choose a vegetarian or even a vegan diet and still meet their protein needs — but I am not necessarily pro- or anti-vegetarian. I would recommend two things: eating less protein in general and shifting the source of some protein from animal to plant foods. Keep in mind that, beyond protein, this shift to a more plant-based diet is now consistent with the recommendations of every public health organization regarding improving human health. In our paper, we modeled the impact of individuals consuming 25 percent less protein, and also shifting 25 percent of the remaining protein that they consume from animal to plant foods. For Americans, that would mean still getting most of their protein from animal foods, about a 60-40 split. By our estimates, that 25 percent-less-and-25-percent-shift recommendation would result in 40 percent lower carbon dioxide emissions from food production-related sources, which would be equivalent to about 8 percent of the greenhouse gas emissions reductions originally pledged by the United States under the Paris Climate Agreement. The shift would also equate to a 10 percent decrease in methane emissions and a 25 percent decrease in water consumption contributions.

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Packard nurse aims to advance patient care through research

By Erin Digitale

When Kimberly Pyke-Grimm began studying how teens and young adults with cancer make decisions about their medical care, her years as a pediatric-oncology nurse shaped her research. So did her years as a mother of three.

“I feel strongly about contributing to child health because two of my children were born with heart disease,” she said. “I want to be making a difference in giving other children the best care because my children received it.”

A pediatric oncology nurse for more than 30 years, Pyke-Grimm recently earned a PhD in nursing from the University of California-San Francisco. Today, she is one of two nurses working at Lucile Packard Children’s Hospital Stanford. Her work is part of a larger trend in which more nurses are conducting clinical research, bringing their unique perspective from the front lines of clinical care to the research enterprise.

“In addition to maintaining their own body of research, our nurse-scientists support the development of future scientists, help our bedside nurses evaluate clinical questions and practice changes, and offer training to our nurses across the organization,” said Kelly Johnson, PhD, RN, vice president of patient care services and chief nursing officer at Packard Children’s. “It’s really important to have that resource for the support of our clinical program and advancement of our scientific programs. It fits in with our organization’s strategic plan and our model of nursing excellence.”

At home in research

Pyke-Grimm now devotes 40 percent of her time to research at Packard Children’s and 60 percent to patient care as a clinical nurse specialist at the hospital’s Bass Center for Childhood Cancer and Blood Diseases. Her work includes the responsibilities and routines of any scientific pursuit — seeking funding, carrying out and publishing studies, and mentoring junior investigators. But she is doing all of that through the lens of a nurse.

When Pyke-Grimm began working in pediatric oncology, she was struck by the painful uncertainties families faced as they made treatment choices for their children. Patient's worries were magnified when a young child in a clinical trial, grapple with the choice between different cancer treatments or battle complications associated with a child's diagnosis of life care.

“As a bedside nurse, I really bore witness to them struggling to make some of those decisions,” Pyke-Grimm said.

In 1988, Pyke-Grimm and her husband, Paul Grimm, MD, now a pediatric nephrologist at Packard Children’s, moved from their home in Canada to Southern California, where they both attended UCLA. He completed a fellowship in pediatric transplant immunology, and she earned a master’s degree in nursing, an experience that hooked her on nursing research. When the couple moved to Winnipeg, Canada, in 1991, Pyke-Grimm collaborated with Lesley Degner, a professor of nursing at the University of Manitoba. Degner studied decision-making in adults with cancer. Together, she and Pyke-Grimm extended these investigations to parents of young children.

“I was so very fortunate, working with Lesley,” Pyke-Grimm said. “I felt like, this is my home: decision-making research.”

During the 1990s, Pyke-Grimm published studies showing that, while most parents wanted to collaborate with their child’s oncolgists to make treatment decisions, some preferred more passive or active roles. Furthermore, the information parents wanted from their doctors varied with their decision-making style. For instance, the most active decision-makers needed the most information about possible treatment side effects.

“The findings can help caregivers tailor medical discus- sions to families’ individual needs when making de- cisions about their child’s treatment. It’s one example of how research conducted by nurses can refine patient care,” Pyke-Grimm said. “Nurses think about the human response to things because we spend so much time with patients in very private and stressful situations,” Pyke-Grimm said. “Almost every day that I work as a clinical nurse specialist, I think, ‘We should study that’ or ‘Why is it we’re doing it this way?’”

Helping teens, young adults with cancer

Pyke-Grimm and her family, which now included three children, moved to the Bay Area in 2007. She began working at Stanford in 2011 and started pursuing a PhD fellowship later. She continued to study decision-making, including that of Packard Children’s pa- tients, but focused her dissertation on teens and young adults with cancer; they face a unique set of challenges.

“Teenagers in particular have not kept pace with their older and younger peers,” Pyke-Grimm said. “We also know this age group is not as adherent with their medi- cation; their nonadherence rates are reported at 20 to 60 percent.”

These young people may also have trou- ble balancing their medical needs with worries about how much to rely on their parents, returning to school after illness, changes to their bodies and maintaining friendships.

“We hope that if we work on decision-making, com- munication and self-management, there will be oppor- tunities to increase their adherence to treatment, and maybe even increase enrollment in clinical trials and improve survival rates,” Pyke-Grimm said. Her work, which has uncovered information about what types of decisions teens want to be involved in, is now being sub- mitted for publication. Of the next steps, she said, is to test decision-making interventions based on what she has learned to see if they improve patient outcomes.

Integrating research into culture of healing

“If we’re looking at the safest and best practices for patient care, nurses are uniquely positioned to do that because of how we interact with the whole medical team, as well as with patients and families,” Johnson said, adding that Pyke-Grimm’s work fits into a larger research goals being pursued by Packard Children’s to improve the impact of healing environments on patient outcomes.

Pyke-Grimm is inspired by the research collabora- tions she’s forged with Stanford experts from a variety of backgrounds, including specialists in pediatric oncol- ogy, precision health, adolescent medicine and palliative care.

“It is such a rich environment,” Pyke-Grimm said. “Having colleagues like that just down the hall, who are excited about research and will say, ‘We really need to look at this; there’s a gap here,’ is pretty amazing.”

She is encouraging the careers of junior nurse-scienc- tists, mentoring a fellow in evidence-based practice and working to bring more nurses into her research projects. And she is a resource for nurses who are wondering if they want to add a research element to their careers.

“I tell them that this is making a difference in a dif- ferent way,” she said. “It’s not instant gratification like patient care, where you might give pain meds and a pa- tient’s pain quickly goes from an 8 out of 10 to a 2 out of 10. Research is a long process, but the benefits can be huge. It can really make a difference to how we give care in the future.”

Positive mindset helps with allergy treatment, study finds

By Melissa De Witte

For children undergoing a promising peanut-allergy treatment that involves taking small doses of the allergen, un- comfortable side effects can induce anxiety, even to the point of skipping doses or dropping treatment entirely.

But guiding young patients to the mindset that uncomfortable side effects are a sign that the therapy is working can help reduce anxiety, according to a new study from Stanford University.

The study, published Jan. 28 in Jour- nal of Allergy and Clinical Immunology: In- fants and Children, looked at how children perceived mild reactions to the treatment as useful, they were less anxious about the reactions, and also less likely to skip doses. They were also less likely to experience side effects at the end of the research when real peanuts were introduced.

Promising treatments

Almost 6 million American children and adolescents have food allergies. Oral immunotherapy is an emerging treatment whereby gradually patients consume tiny doses of allergen until they build tolerance to it.

During treatment, patients can expe- rience a mild but lingering state with an itchy mouth or congestion. These reactions are evidence that the treatment is working, but for some patients, it can cause anxiety because of its asso- ciation with a larger, more severe allergic reaction.

“Many of the decades of clinical trials that oral immunotherapy is likely effective in protecting from accidental exposure to food allergens,” said Kari Nadeau, MD, PhD, professor of medi- cine and of pediatrics and director of the Scan N. Parker Center for Allergy and Asthma Research at Stanford. “But we thought that people might often miss this mindset about symptoms, only seeing the negative aspects of symptoms. So we thought an intervention that made this mindset salient could have a lot of potential.”

For the study, the researchers recrui- ted 50 participants ages 7-17. Fami- lies were randomly split into two groups: a “symptoms as side effects” mindset and a “symptoms as positive signals” mindset. Both groups received identical treatment instructions and were trained to use medications, such as see PEANUT, page 8
Antibody could increase cure rate for blood, immune disorders

By Krista Conger

An antibody-based treatment can gently and effectively eliminate disease blood-forming stem cells in the bone marrow, according to a new study about the regeneration of healthy stem cells, according to a study in mice by researchers at the School of Medicine.

The researchers believe the treatment could circumvent the need to use harsh, potentially life-threatening chemotherapy and radiation during bone marrow transplantation, vastly expanding the number of people who could benefit from the procedure.

“There are many blood and immune disorders that could be cured by a transplant that we can’t do today,” said Agnieszka Czechowicz, MD, PhD, professor of medicine at Stanford. “But the pre-treatments necessary to get the healthy cells to transplant effectively are so toxic that we can’t offer this option to many patients. A treatment that specifically targets only blood-forming stem cells would allow us to potentially cure people with diseases as varied as sickle cell disease, thalassemia, autoimmune disorders and other blood disorders.”

Shizuru is the senior author of the study, which was published online today in Blood. Postdoctoral scholar Wendy Pang, MD, PhD, and assistant professor of pediatrics Agnieszka Czechowicz, MD, PhD, share lead authorship of the work.

The study is one of two recently co-authored by Shizuru and published online today in Blood by researchers at the School of Medicine who investigated a method of inducing tolerance without the need for chemotherapy and radiation during bone marrow transplantation. One study, led by researchers at the Institute for Stem Cell Biology and Regenerative Medicine at Stanford, found that an antibody to a protein on blood-forming stem cells could continue to defend against various pathogens for transplant, vastly expanding the number of people who could benefit from the procedure.

They found that the antibody blocked the growth of both healthy and diseased cells. These results are particularly important because other studies in animals and patients have shown that replacing blood-forming stem cells with a donor’s blood-producing cells can promote the immune acceptance of tissues from that donor. Unfortunately, current methods of eliminating blood-producing stem cells rely on toxic levels of chemotherapy or radiation, or both, that not only have acutely damaging and long-lasting side effects, but also leave the recipient vulnerable to infection while the transplanted cells engraft.

“SR1 directly targets the disease-initiating cells for elimination in the mice, even though these cells typically have a significant competitive advantage,” Pang said. “But there is no other cure for MDS.”

Judith Shizuru is senior author of the study, which found that an antibody to a protein on blood-forming stem cells may allow bone marrow transplants without the need for chemotherapy and radiation.

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Dengue continued from page 1

gressing to a severe form of the illness.
Every year, between 200 million and 400 million people in tropical and subtropical regions of the world contract dengue fever, and about 500,000 of those cases are fatal. For the most part, people with the disease recover after receiving some fluids and a few days rest, said Purvesh Khatri, Ph.D., associate professor of medicine and of biomedical data science. “But there’s a smaller subset of patients who get severe dengue and right now we don’t know how to tell the difference.”

Anywhere from 5 to 20 percent of dengue cases will advance to severe. Currently, the standard of care boils down to watching and waiting; to diagnose severe dengue, doctors wait to observe specific symptoms and results of laboratory tests that typically emerge in the late stages of the disease. “These practices are not nearly sensitive or accurate enough, and some patients end up admitted to the hospital unnecessarily, while others are discharged prematurely,” said Shirit Einav, MD, an associate professor of medicine and of microbiology and immunology.

Using their newly identified set of genes as a foundation, Einav and Khatri aim to identify predictive biomarkers that can help doctors reliably gauge the likelihood of severe dengue in patients who are newly symptomatic and use that information to provide more accurate care to help guide therapeutic clinical studies and, in the future, to guide treatment decisions.

A paper detailing the study’s findings was published Jan. 29 in Cell Reports. Einav and Khatri are co-senior authors. Graduate student Makeda Robinson, MD, and former research associate Timothy Sweeney, MD, PhD, share lead authorship.

Continued from page 1

Mining old data

Adept at sifting out new findings from old data, Khatri used previously published papers, which reported information on about 450 individuals collectively, to identify the severe-dengue gene set.

“I see this as a unique approach,” Einav said. “This prediction method is more of a continuum rather than a binary,” Khatri said. “To make sense of the continuum, the researchers developed a score that accounted for this gene-expression variability, essentially evaluating the patients’ risk for severe dengue based on dips and peaks of expression in these 20 genes. The higher the score, the higher the risk for severe dengue.

“Of course, these population samples are small, and we want to confirm our findings in larger cohorts,” Khatri said. The researchers plan to conduct larger trials as they aim to bring the evaluation into clinical use. “They’re already expanding trials into Paraguay. With a larger cohort, there’s also an opportunity to refine the signature; we could potentially bring down the number of genes,” Einav said. “There’s no perfect but, by refining it, the score becomes more sensitive and accurate enough, and some patients end up admitted to the hospital unnecessarily, while others are discharged prematurely,” said Shirit Einav, MD, an associate professor of medicine and of microbiology and immunology.

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Shirit Einav and her colleagues have identified a gene-expression pattern that predicts which patients infected with dengue are at highest risk for developing a severe form of the illness.

Sex continued from page 1

The findings are likely to apply to humans, Shah said, because we share with mice much of the same hard-wired brain circuitry they use for recognizing a stranger’s sex and how human studies of this circuitry indicate significant structural and functional differences between men and women.

“All social and sexual encounters are predicated on first correctly identifying the sex of the other agent,” Shah said. “It’s a fundamental decision animals make.”

Where and how mammals make such decisions was completely unknown prior to this study. But the investigators did have some ideas about where to start looking.

Indispensable subset of neurons

Numerous tissues responsive to sex hormones produce aromatase, an enzyme that converts androgens into estrogens — the active form of these sex hormones inside many cells. Aromatase turns up in about a half-dozen mouse-brain regions that Shah and his colleagues identified a decade ago. Some of these brain regions differ in their anatomy, physiology and behaviors they govern, depending on whether the brain is that of a male or a female.

One such region is called the bed nucleus of the stria terminalis. This structure is twice as large and more densely populated with neurons in men than in women. Human studies have revealed different patterns of gene-activation levels in men versus women’s bed nucleus of the stria terminalis — a reliable clue that this structure’s function differs by sex.

A tiny fraction of this structure’s neurons, called AB neurons, produce aromatase. It’s these cells, about 1,000 on each side of a mouse’s 75-million neuron brain, that Shah’s team has tied to sex recognition. “Prior to this study, AB neurons were for the most part unexamined,” he said. “They’ve been particularly hard to study because they’re interspersed among other superficially identical-appearing neurons.”

But Shah’s group has developed tools that let them both monitor signaling activity in AB neurons in freely moving mice and remotely stimulate or inhibit activity in just those neurons. They used these tools to study and manipulate the AB neurons of male mice that had never been exposed to a female mouse besides their mothers and sisters during their first few weeks of life. Immediately after being weaned (and well before puberty), they’d been transferred to a neutral housing and, then, several days prior to the experiments, to solo housing.

It’s long been known that a male mouse in its own turf, whether it’s sexually naïve or experienced, responds predictably to the intrusion of another individual. But that response depends on the stranger’s sex, Shah said. “If it’s a female, the resident male will try to woo her. If it’s a male, he’ll pick a fight.”

Hard-wired differences

As expected, when the researchers introduced a female into the naïve male’s habitat, not much more than a few minutes of sniffing and exploring passed between the two. But if the naïve male was transferred to another room where they introduced another male into the bachelor pad, the resident male went on the offensive. “This increase was much greater the stranger was a female,” said Einav. Regarding the sexual behavior following the resident male’s recognition of a female, those neurons got even more activated.
Robert Jackler says Juul spurs ‘nicotine arms race’

When Juul first put its e-cigarettes on the market, it brought a new level of nicotine e-liquids that were 1 to 2 percent nicotine by volume, whereas Juul pods are marketed as containing 5 percent (by weight), which is equivalent to 5.9 percent by volume — three times more concentrated than what we’ve seen in the market before. The disparity caused another e-cigarette manufacturer to increase the amount of nicotine in their devices and pods, igniting something that Robert Jackler, MD, professor and chair of otolaryngology and the Edward C. and Amy H. Sewall Professorship in Otolaryngology, refers to as “a nicotine arms race.”

1 How has Juul changed the norms of e-cigarette production?

JACKLER: The astounding financial success of Juul, which is valued at $38 billion after only 3½ years on the market, has led to an upswell of devices that emulate its high-tech appeal, small size and stealthiness.

Until recently, most e-cigarette liquids carried 1 to 2 percent nicotine, with a few considered “super high” at 3 percent, intended for the two-pack-a-day smoker. In 2015, Juul introduced a 5 percent nicotine vaporizing liquid with a novel chemistry — nicotine salts — which improved palatability, enabling higher concentrations of nicotine without undue bitterness. Following Juul’s phenomenal success, numerous knockoff devices were introduced that emulated, or even exceeded, Juul’s very high nicotine level. Also problematic, the nicotine percentage is inconsistently portrayed on labels. Juul, unlike most e-liquid brands, measures its nicotine content by weight rather than by volume. For example, the nicotine level in Juul’s e-liquid is 5 percent by weight versus 5.9 percent by volume. This inconsistency in labeling the nicotine concentration is likely to mislead consumers.

In terms of acute health risks, Juul and its high-nicotine emulators are more efficient at delivering nicotine than conventional cigarettes. This makes them potentially addictive, especially to nicotine-naïve teens.

More than 99 percent of high-nicotine products, meaning those with nicotine concentrations of 5 percent or higher by volume, in bulk — without a child-resistant cap, contains 6 teaspoons of nicotine, which is considered enough to smoke for about 40 cigarette packs. All of these products come in multiple, youth-appealing sweet and fruity flavors, often in colorful bottles with a picture of cookies, candy or other dessert treats. Concentrated nicotine is highly toxic, and these large-volume nicotine bottles are a poisoning risk for children.

The lethal dose for a toddler, if ingested, is a bit more than 1 milliliter of e-liquid with a 5 percent nicotine content. The typical 30 milliliter bottle, which almost never comes with a child-resistant cap, contains 6 teaspoons of nicotine concentrate. If ingested, it’s enough to kill five toddlers — the full bottle an entire class of 25 pre-schoolers.

3 Juul is often marketed as a device that will help inviduals addicted to cigarettes quit. Is it actually effective? Are there ramifications one should recognize?

JACKLER: The body of data regarding the possible role of e-cigarettes in traditional cigarette cessation is accumulating. While results across studies have been variable, a recent prospective study published in The New England Journal of Medicine reported 18 percent success in quitting combustible cigarettes with e-cigarettes, as opposed to 9.9 percent with other forms of nicotine replacement therapy such as patches and gums or behavioral support. Others have warned that smokers who use e-cigarettes to satisfy their nicotine urges in places where smoking is banned have deepened their nicotine addiction. For at least some dual users (both cigarettes and e-cigarettes) adding e-cigarettes makes quitting less likely.

Whether or not high-percent nicotine devices are more effective in transitioning cigarette smokers has yet to be established by well-designed research, but anecdotal evidence suggests that they may be more effective than lower-nicotine e-cigarettes. The rapid rise in nicotine blood levels following a puff from Juul more closely mimic the physiology of smoking, and it is unclear whether or not higher-nicotine devices are more effective for heavy smokers who are trying to quit smoking.

5 How can public health or government officials better control the sale of higher concentration nicotine solutions?

JACKLER: High-nicotine vapor products often come in sweet and fruity flavors, such as mango or gummy bear. One policy option would be to ban youth-appealing flavors from all nicotine-containing e-liquids and allow only unsweetened tobacco flavor to accompany nicotine. This would help to reduce the appeal of these products among youths while retaining a product acceptable to adult smokers seeking to transition from cigarettes.

Another regulatory option would be to cap the amount of nicotine present in e-cigarettes. The amount of nicotine in Juul pods that is sold in the United States (59 milligrams of nicotine per milliliter of e-liquid) would not be permitted in Europe or the United Kingdom, which have adopted limits of 20 milligrams of nicotine per milliliter of e-liquid. If the U.S. adopted this standard of 20 milligrams per milliliter, it would almost certainly reduce the tendency of e-cigarettes to act as a gateway to youth nicotine addiction. However, it may also reduce their efficacy in cigarette-smoking cessation.

“Depressed patients are at greater risk for pain, and we’re failing them because we’re not educated enough about the drugs we’re prescribing,” he said.

Other Stanford co-authors of the study are research scientist Imon Banerjee, PhD; Keith Humphreys, PhD, professor of psychiatry and behavioral sciences; research assistant Matthew Mason; Albert Susanto and Al-exandra Lobdell.

The work was funded by the National Institutes of Health. Stanford’s departments of Neurobiology and of Psychiatry and Behavioral Sciences also supported the work.

Sex

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more excited. By contrast, their activity subsided during the ensuing fights with a male.

Even neutering a male didn’t affect the AB neurons’ ability to distinguish between the two pheromone patterns or further supporting the idea that this ability is developmentally hard-wired.

When a subject was tested, the interrogators experimented by AB neurons’ action during a male resident mouse’s en-counter with a stranger of either sex, he morphed into a kind of wimp due to his suppressed sex-recognition capacity. “He wouldn’t fight with the males, and he wouldn’t mate with the females,” Shah said. “Females apparently use a different neural system to recognize sex of other females.”

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Opioids

continued from page 1

milder than hydromorphone, whose trade names include Dilaudid and Exalgo, or morphine, Carroll said.

“The prescribing of hydromorphone has more to do with history and perception,” he said. “The liver converts hydromorphone into hydromorphone and converts codeine into morphine, so the result is the same.”

Carroll added that depressed patients’ complaints about pain after receiving opioids are often dismissed because of their mental state, when the problem lies in an unfortunate drug interaction.

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The work was funded by the Agency for Health Care Research and Quality. Stanford’s departments of Psychiatry and Behavioral Sciences, of Management Science and Engineering, and of Biomedical Data Science also supported the work.
Four faculty members are appointed to endowed professorships

TIMOTHY CORNELL, MD, professor of pediatrics, was appointed the Chambers-Okamura Professor of Pediatric Critical Care Medicine, effective Dec. 4. His research interests include the role of epigenetics in the regulation of inflammation and the use of molecular biomarkers and precision medicine to improve outcomes for critically ill children.

The professorship was established with a gift from Jeffrey Chambers and Andrea Okamura to support the division chief of critical care in the Department of Pediatrics. Chambers, who earned an MBA from Stanford, is chair of the board of directors at Lucile Packard Children’s Hospital Stanford.

KEVIN SHEA, MD, professor of orthopaedic surgery, was appointed the Chambers-Okamura Endowed Professor of Pediatric Orthopaedics, effective Dec. 4. His research interests include the role of patient safety in the healthcare system, with the aim of improving clinical care.

The professorship was established with a gift from Jeffrey Chambers and Andrea Okamura to support a faculty member with a focus on pediatric orthopaedics in the Department of Orthopaedic Surgery.

JOANNA WYSCOSKA, PhD, professor of chemical and systems biology and of developmental biology, was appointed the Loory Lokey Professor, effective Dec. 4. Her research examines how gene regulation and expression are related to human development, evolution and disease.

The professorship was established with a gift from Loory Lokey and an anonymous donor to support a basic science faculty member who specializes in stem cell research. Lokey, a Stanford alumnus and significant donor, founded Business Wire, which distributes press releases and regulatory disclosures.

TONY WYSS-CORAY, PhD, professor of neurology and neurological sciences, was appointed the D.H. Chen Professor II, effective Dec. 4. His research focuses on brain aging, neurodegeneration and Alzheimer’s disease.

The professorship was established with funds from the D.H. Chen Foundation and an anonymous donor to support a School of Medicine faculty member in the neurosciences.

Neuroscientist Liqun Luo, PhD, has been honored with an award from the National Academy of Sciences for his pioneering research into neural circuits of invertebrates and vertebrates. The annual $100,000 award recognizes innovations in medical devices that enable minimally invasive angioplasty procedures in which uncomfortable side effects indicate treatment effectiveness, such as flu vaccines or possibly procedures in which uncomfortable side effects indicate treatment effectiveness, such as flu vaccines or possibly chemotherapy.

“My hope is that this study sparks a wave of similar experiences in the manner in which medical treatment are delivered,” Crum said.

Meanwhile, the researchers hope that medical providers can use this intervention into practice.

“We hope that this intervention can be successfully adapted into clinical practice to help [oral immunotherapy] practitioners reduce anxiety among their patients and to make this very promising treatment even more effective and stress-free for patients and their families,” Howard said.

In the long term, the researchers think that these findings have promise for improving other challenging courses of treatment.

Graduate student Kate Leibowitz is the study’s other lead author.