A new psychiatric residential treatment facility will open across from Mayo Clinic Hospital — Rochester, Saint Marys Campus, in Rochester, Minnesota, in early 2018. Named John E. Herman Home and Treatment Facility, in collaboration with ClearView Communities, it will comprise two homes, housing eight patients each, with a treatment center and community area connecting the residences (Figure).

Brian A. Palmer, M.D., M.P.H., a psychiatrist at Mayo Clinic in Rochester, Minnesota, and the new facility’s medical director, believes this home will fill a care gap for patients who need psychiatric care, especially in the region. “There are short-stay psychiatric hospitals, but residential treatment in psychiatry is a care level not widely available,” he says. “We think this type of care will be able to bend the trajectory, particularly at the start of illness and in younger patients.”

Mayo Clinic’s Department of Psychiatry and Psychology will begin accepting referrals to the home in October 2017, and expects to draw interest from providers and patients nationwide. Appropriate patients include those with mood disorders, psychotic disorders or personality disorders. Residents need to be stable, nonviolent and able to benefit from a longer term treatment focused on community integration and functional recovery.

The new facility’s program will provide patients with a comprehensive assessment and individualized plan to help them achieve functional and vocational recovery. The facility’s services will include medication management, evidence-based group and individual psychotherapy, vocational support, and family support. An employment specialist will help residents identify vocational goals, guide them as they look for jobs or volunteer work, and provide support to maintain successful employment.

Living at the home also will be part of the treatment, offering residents an opportunity to become part of a functioning community. To that end, they will make their own meals, maintain living areas and engage in healthy daily activities with staff support.

Two care tiers will be available: a higher care level, averaging a six-month stay, including intensive care with more supervision, and a lower care level for about six to eight additional months, where residents will have more autonomy, less intensive care and meaningful involvement in the community.

Staff for the home will include the medical director, clinical director, program manager, employment specialist, licensed therapists, a nurse and round-the-clock recovery coaches.

The care model is based on a collaboration with ClearView Communities, a residential rehabilitation program for adults with severe mental illness in Frederick, Maryland, founded by benefactor the Sylvan C. Herman Foundation. This model and its principles will combine with Mayo Clinic’s expertise at the new facility, named in memory of Sylvan Herman’s son.

“The treatment model prioritizes functional recovery — from making meals in the residence to obtaining competitive employment,
Acamprosate: Seeking Individualized Treatment for Alcoholism

For more than a decade, acamprosate has been widely used in the United States for treatment of alcohol dependence. The medication is known to reduce some patients’ cravings and prolong abstinence. However, only a subset of patients responds to acamprosate, and predictors of response have yet to be fully identified.

Researchers at Mayo Clinic’s campus in Rochester, Minnesota, have made significant progress in elucidating acamprosate’s mechanism of action, paving the way for more-individualized treatment of patients with alcohol use disorders (AUDs).

In a study published in the Journal of Clinical Psychopharmacology in 2016, the Mayo Clinic researchers found that acamprosate can normalize a hyperglutamatergic state in recently withdrawn patients with alcohol dependence. Before treatment, study participants with alcohol dependence had significantly elevated levels of anterior cingulate cortex glutamate compared with controls. Four weeks of acamprosate treatment reduced glutamate levels — an effect that wasn’t observed in study participants who chose not to take the medication. Mayo Clinic’s expertise in neuroradiology facilitates the measurement of glutamate levels in the brains of clinical study participants.

The findings follow the Mayo Clinic researchers’ discovery of genetic markers that might identify patients who would benefit from treatment with acamprosate. That international study, published in Translational Psychiatry in 2014, was the first report of a replicated association of genetic markers with the length of abstinence in patients with alcohol dependence treated with acamprosate.

“Our translational research projects directly reflect problems of patients we treat in our clinical practice,” says Victor M. Karpyak, M.D., Ph.D., a consultant in Addiction Medicine and director of Addiction Services at Mayo Clinic’s campus in Minnesota. “If we can reliably identify potential responders to acamprosate, we can improve treatment outcomes for these patients and consider alternative treatment options for the others.”

“We are committed to developing tools to help clinicians better individualize their treatment of patients,” adds Mark A. Frye, M.D., chair of Psychiatry and Psychology at Mayo Clinic’s campus in Minnesota. “We want our clinical research trials to make an impact on what we do in our clinical practice every day.”

The search for biomarkers

At Mayo Clinic, translational research is promoted through close collaboration across specialties. Dr. Frye notes that a significant number of patients with AUDs have mood disorders and may self-medicate with alcohol in times of stress and negative affect. “We have strong programs in both addiction and mood disorders. That overlap prompted our thinking about the merits of acamprosate, which can relieve cravings triggered by negative affect,” Dr. Frye says.

Mayo Clinic has a strong commitment to basic science laboratory research that has applications for psychiatric studies. “Team science is an
important part of our success,” says Joanna M. Biernacka, Ph.D., director of Mayo Clinic’s Psychiatric Genomics and Pharmacogenomics Program. “In addition to clinicians, we have scientists who do basic research in pharmacogenomics, metabolomics, clinical neurosciences and radiology, as well as statisticians and data analysts dedicated to analysis of psychiatric clinical and biomarker data.”

The psychiatric genomics group played an important role in Mayo Clinic’s discovery of genetic markers associated with the results of treatment with acamprosate. That work was a candidate gene study; candidate genes were selected using a pathway-based approach to systematically investigate genes involved in encoding enzymes that affect levels of glutamate and other neurotransmitters in the brain that may be involved in acamprosate-associated treatment outcomes in human or animal studies.

“Candidate gene studies are notorious, however, for finding false positives that cannot be replicated. It’s very exciting that our findings were replicated,” Dr. Biernacka says. “Nonetheless, a single biomarker doesn’t have enough predictive accuracy to select people who will or will not respond to acamprosate. We certainly have a long way to go.”

To further identify pharmaco-metabolomic biomarkers of acamprosate results, the Mayo Clinic researchers analyzed serum samples from 120 subjects with alcohol dependency, including 71 who maintained continuous abstinence and 49 who used alcohol during 12 weeks of acamprosate treatment. The study, published in *Translational Psychiatry* in 2015, found that baseline serum glutamate levels were significantly higher in responders compared with nonresponders, suggesting that among patients who respond to acamprosate, the medication reduces elevated serum glutamate levels.

“Considering the complexity of alcohol dependency, there is no single solution for this disease,” says Doo-Sup Choi, Ph.D., director of the Samuel C. Johnson Genomics of Addiction Program and a molecular pharmacologist in Molecular Pharmacology and Experimental Therapeutics at Mayo Clinic. “This elevated glutamate in serum aligns with our finding with elevated glutamate in the brain. Our goal is to continue to fill in gaps — to find and replicate genomic and metabolomics biomarkers for response to acamprosate so that ultimately we can individualize treatment for patients.”

“Acamprosate came to market because of well-designed, placebo-controlled trials with hundreds of patients,” Dr. Frye adds. “So when I write a prescription for acamprosate, I’m prescribing a medication that is evidence-based. But the individual biology of the patient I’m treating wasn’t part of the clinical trials that led to evidence-based approval. That, to me, is what individualized medicine is all about — using drugs that are already available, but with greater precision.”

*For more information*


**Precision Medicine and Antidepressants**

Over the past decade, precision medicine — care designed to optimize therapeutic effect for individual patients — has made significant strides in medical specialties such as oncology. Less progress has occurred in psychiatry, as the neuroscience of specific psychiatric illnesses is generally less defined than the genetics of particular cancers.

Mayo Clinic is committed to applying precision medicine to psychiatry. Antidepressants are among the most commonly prescribed medications in the United States, and it is increasingly recognized that genetic variations in patients may contribute to the variability in effectiveness and adverse-effect toxicity profile of these drugs.

Researchers at Mayo Clinic’s campus in Rochester, Minnesota, have proposed pharmacokinetiic and pharmacogenetic prescribing guidelines for antidepressants, as a template for psychiatric precision medicine. In a literature-review study published in *Mayo Clinic Proceedings* in 2016, the researchers note that providing more-precise pharmacotherapeutic recommendations for individual patients — beyond the evidence base of large-scale clinical trials — can potentially improve treatment.

“We are learning how complex the interaction is between genes and the environment and
how those interactions can lead to psychiatric illness,” says Malik M. Nassan, M.B.B.S., a psychiatrist in the Depression Center at Mayo Clinic’s campus in Minnesota. “Currently there is actionable data on the pharmacokinetics of antidepressants. Based on a patient’s genetic code for relevant metabolic enzymes, it is possible to select the antidepressant that can provide the needed efficacy with the least side effects for that particular patient.”

Metabolizer categories

The researchers focused on cytochrome P450 (CYP) genetic variation, which is known to influence the way in which selective serotonin reuptake inhibitors are metabolized. Specifically, the researchers analyzed the approximately 140 major genetic allelic variants encoding for two CYP-metabolizing enzymes, CYP2D6 and CYP2C19. Fluoxetine, paroxetine, and the serotonin and norepinephrine reuptake inhibitor venlafaxine are largely metabolized by CYP2D6. Citalopram and escitalopram are primarily metabolized by CYP2C19.

The genetic variations were categorized into four main metabolizer phenotypes:
• Poor
• Intermediate
• Normal
• Ultrarapid

Ultrarapid metabolizers potentially have lower bioavailability of the medication and thus possibly lower efficacy. Poor metabolizers’ inability to produce a functional enzyme leads to an increased drug plasma level with a potentially increased rate of adverse effects.

“We know the side effects emerging from different antidepressants. These side effects can affect compliance and also possibly endanger patients,” Dr. Nassan says.

For example, citalopram has been associated with a dose-dependent QTc interval increase. The Food and Drug Administration (FDA) initially approved dosing of no greater than 40 milligrams (mg) a day, later revising that dosage to no greater than 20 mg a day. The FDA also identified CYP2C19 poor metabolizers as being a risk factor for QTc prolongation.

The Mayo Clinic study cites the report of a 34-year-old patient with major depressive disorder who was taking venlafaxine at the time of death; the report’s authors concluded that the cause of death was likely cardiac arrest due to a high blood concentration of venlafaxine attributed to CYP2D6 poor metabolizer phenotype.

“Having pharmacokinetic information prior to prescribing an antidepressant can help in prescribing a safer medication for the patients, and possibly adjusting the dose based on the genetic structure,” Dr. Nassan says.

At Mayo Clinic, pharmacokinetic and pharmacogenetic data are incorporated into clinical decision support systems. For patients who have had genotype testing, test results are included in their electronic health records. If a patient is at risk of a drug-gene interaction, a warning appears when the clinician enters the prescribed medication into the patient’s electronic record.

“At this point and based on the current data, the alert will suggest changing to another medication that’s metabolized differently, which likely has a similar efficacy but lower rate for side effects,” Dr. Nassan says.

Mayo Clinic doesn’t routinely conduct genetic testing for all patients, due partially to insurance coverage issues. “However, if the genetic information is in the record, then using it to make a more informed decision on which antidepressant to select is just common sense,” Dr. Nassan says. That genetic information will increasingly be available, as many Mayo Clinic patients participating in clinical trials undergo genetic sequencing.

“This is where medicine is moving forward,” Dr. Nassan says. “In the near future, with the constant decrease of genetic testing cost, better insurance coverage and the expansion of a body of evidence further supporting the clinical significance, genotyping will become a routine test prior to prescribing relevant antidepressants and, by extension, other psychotropics to all patients.

“We need more translational research that links advances in clinical neuroscience and genetics research to the clinical practice of psychiatry, in order to make evidence-based personalized psychiatry practice a reality,” he adds.

For more information