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Researchers develop new, automated, powerful diagnostic tool for drug detection

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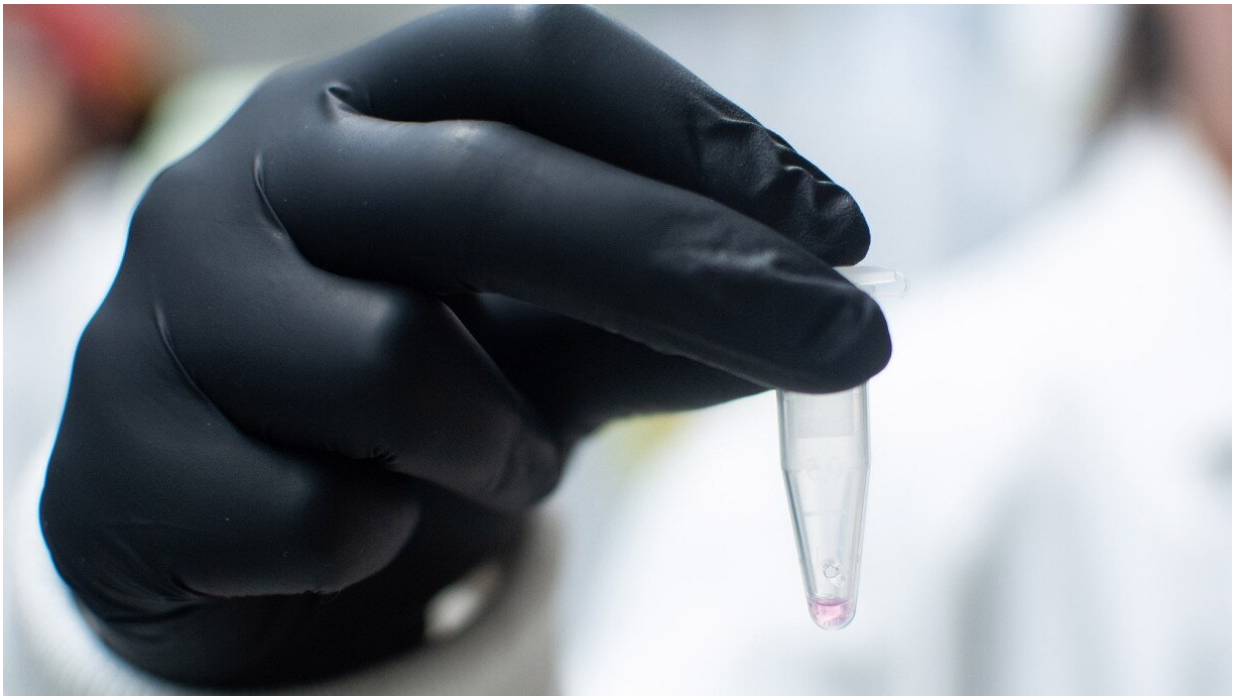

Brown senior Emma Rothkopf shows what a 20 microliter sample looks like. Credit: Brown University

In recent years, a mass spectrometry process that can detect the amounts of drugs in a biological sample, such as blood, has become a powerful diagnostic tool for helping medical professionals identify and monitor levels of therapeutic drugs in patients, which can cause unwanted or dangerous side effects.

Holding back this technique—which is called liquid chromatography tandem mass spectrometry or LC-MS/MS for short—is that it often requires relatively large biological samples and a number of complicated steps that must be done by hand to prepare samples for analysis.

At Brown University, a team of biomedical engineers has been working to make this time-consuming process simpler and much more automated, a key ingredient to the technique being widely adopted by clinicians. The researchers shared their results in *Scientific Reports* on Monday, Feb. 6.

In the study, they present a robust new method for accurately measuring and identifying eight antidepressants most commonly prescribed to women: bupropion, citalopram, desipramine, imipramine, milnacipran, olanzapine, sertraline and vilazodone.

The method does just what the researchers hoped. It is able to identify and monitor these drugs from small biological samples—20 microliters each, which is about the equivalent of blood taken from a prick. The method is also able to be done almost entirely by liquid-handling robots found in most clinical mass spectrometry labs.

"We designed our method and put together kits so that once the samples have been collected, they can be put in a computer program for a robotic liquid handler, and all the user essentially has to do is take off the caps, press some buttons, and it will go start to finish," said lead author Ramisa Fariha, a Brown Ph.D. student working in a microfluidic diagnostics and biomedical engineering laboratory led by Brown professor Anubhav Tripathi.

Once the samples are ready, the user puts them through the mass spectrometer, which breaks the sample down into tiny fragments that contain tell-tale signs of the drugs they are looking for. The method's

accuracy is comparable to other LC-MS/MS-based techniques but has the advantage of a much smaller sample size and is able to be largely automated using the liquid handlers.

These innovations set up the system's immediate potential to be widely translated to clinical settings to help monitor the impacts of drugs prescribed for patients diagnosed with depression, including women experiencing postpartum depression.

"We have made a very big step," said Tripathi, a Brown engineering professor, the lab's principal investigator and an author on the study. "For clinical lab adaptation, you want to reduce the error by humans. The more you automate, the more robustness you get and the more trust there is from doctors."

Depression is a growing global crisis, and women face higher rates of diagnosis than men. The percentage of patients prescribed antidepressants has tripled over the past two decades, and clinicians find themselves at a crossroad between finding the right drug to suit a patient and monitoring the abundance of it in the body, the researchers wrote in the study.

Currently, there are no commercial products in the U.S. to help clinicians directly monitor how much these drugs are present in patients, the researchers noted. Clinicians often end up relying on more qualitative methods, like surveys, because of how obtrusive mass spectrometry methods are to patients in terms of sample size and the time-consuming nature of preparing the samples for the machine.

Tripathi and colleagues in his lab started working on this potential solution in 2021 after they were asked to evaluate a commercial European kit that uses LC-MS/MS to detect drugs in humans. The work has largely been the result of a collaboration between Brown graduate

and undergraduate students who work in the lab.

The researchers, led by Fariha, decided to take a crack at designing their own kit that could be just as accurate but much simpler. They started by identifying some of the most commonly used depressants and from there worked to refine the how the LC-MS/MS technique identifies the drugs, including how much of a sample it needs and establishing a control they could run against actual samples.

After running a barrage of quality control checks, tweaking and testing different methods of measuring the samples at different conditions, the researchers took their entire process for preparing the sample and broke it down so that it could be programmed into a machine that could handle the preparation of the liquids.

The Brown researchers used a JANUS G3 Robotic Liquid Handler in their work but said that clinicians can use simpler or more advanced machines. The team detailed how they programmed their machine in a way that others can easily replicate with their own equipment.

"Every time our lab and our team publishes a paper, we go into the nitty gritty so our results can be easily replicated by others," Fariha said.

The team also created prototype kits that can be sent to clinicians so they can implement the method in their labs. The kits include the chemicals and solvents needed along with a detailed instruction booklet that calls out what clinicians should be on the lookout for based on their own experiences and the numerous tweaks they made during quality control process.

The team—known within the lab as the clinical diagnostics and automation team—plans to work next on automation projects in oncology, such as designing a kit that could detect ovarian cancer.

The automation team has a number of undergraduates who participate—an example of how Brown students collaborate with each other and with faculty to address real-world problems. Emma Rothkopf, a senior concentrating in biomedical engineering and an author on the paper, said the experience was critical in helping her directly bridge concepts she learned in the academic setting to the lab.

"I'd find myself looking at data or doing certain steps and think, 'Oh, my gosh, I learned this in class,'" Rothkopf said.

In addition to Fariha, Tripathi and Rothkopf, other authors on the study include Prutha S. Deshpande, Mohannad Jabrah, Adam Spooner and Oluwanifemi David Okoh. The work was supported by PerkinElmer.

More information: Ramisa Fariha et al, An in-depth analysis of four classes of antidepressants quantification from human serum using LC–MS/MS, *Scientific Reports* (2023). DOI: 10.1038/s41598-023-29229-0

Provided by Brown University