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SPECIAL REPORT

Neuroscience

HOLDING OUT HOPE

Depression in all its various forms is a complex condition, which is why there isn't simply one "happy pill" or even a few options that work consistently for all people or for extended periods; likewise, the complexity and individuality of depression—along with a lack of truly objective diagnostic parameters—makes the search for biomarkers of depression difficult.

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Trying to reframe the depression conversation

BY RANDALL C WILLIS

LOOK AROUND as you read this article. Assuming you're not hidden in a corner somewhere, 7 percent or more of the people you can see have had a major depressive episode within the past year, according to National Institute of Mental Health stats. And more than a third of those people received no treatment for their condition.

An even larger percentage, if not everyone, have had to deal with a loved one or friend who has experienced depression in the past, or does now.

And according to the U.S. Centers for Disease Control and Prevention, at least 80 percent of adults experiencing depression will report some difficulty with their work, home or social lives because of the depressive symptoms.

"When you have depression, you also have comorbidity of depression," says Aptinyx President and CEO Norbert Riedel. "You have sleep disturbance. You have cognitive dysfunction."

And even when a patient's mood symptoms have been stabilized, a significant proportion of people still struggle with these comorbidities, finding it difficult to get back to work or take care of the kids.

Aggravating this situation further, according to Roger McIntyre, executive director of the Brain and Cognition Discovery Foundation, is that the longer someone has depression or the more episodes they have, the less reliable treatments become.

"Something is happening at the neurobiological level that's changing the biology of the brain, making it less cooperative with treatments," he presses. "That is why it is so important for us to have timely early accurate diagnosis and get people on the right treatments."

Unfortunately, clinicians have not had a lot of options from which to choose.

"When you look back in history, you had tricyclic antidepressants in the 1950s and then the SSRIs [selective serotonin reuptake inhibitors] in the 1980s," explains Stephen Peroutka, vice president of global product development and neuroscience therapeutic lead for PPD.

McIntyre recounts cases he has seen where a patient is put on an antidepressant treatment that is only partially effective, but they are left on that same medication for two, three, four years. As he terms it, the patient's depression simply smolders along.

"Can you imagine going on a cancer drug that just has a partial effect on your tumor?" he asks. "Your oncologist says 'just stay on it and in three or four years, we'll see what happens.' No one thinks like that outside of psychiatry."

Alternatively, Riedel offers, the clinician intervenes when the patient experiences side effects or poor response, but to questionable effect.

"They put you on another one and then a third one, but they are all the same class of molecules," he complains. "I'm not sure what we are gaining by experimenting with different molecules of the same class."

This unfortunate scenario may soon change, however, as the understanding of the pathophysiology of depression expands and new insights are resulting in a growing pipeline of novel class candidates, some of which recently received blessing from the FDA.

Expanding repertoire

"The landscape really has changed and has evolved into a much more comprehensive, much more coherent and powerful inflammatory model," says McIntyre. (See also the table "Drugs in development" on page 18.)

The notion that there is an alteration in your serotonin levels has been with us for a long time, he continues, suggesting that most FDA-approved agents for depression are monoamine-based.

"It turns out, however, that a good 30 to 40, maybe 45 percent of people with depression taking Prozac-type drugs do not get better," he claims. "So therefore, one can only conclude that there must be some other target that we can look at."

McIntyre points to the array of preclinical and clinical work showing that disturbances in brain neurochemistry extend well beyond monoamine, impacting other areas such as glutamate pathways, inflammation and neurosteroids.

"This hangs together because glutamate, among other things, plays a key role in brain plasticity, known to be abnormal in depression," he explains. "Moreover, inflammation plays multiple roles involved in plasticity, regulating other neurochemistries like dopamine and serotonin, and having its own direct effect on brain systems relevant to the symptoms that we see in depression."

As proof, he points to drugs being developed to target glutamate and target inflammation, many of which, he suggests, look very promising.

One such candidate is rapastinel, which was licensed to Allergan as a treatment for depression from what is now Aptinyx. The compound is a partial agonist of the NMDA receptor, which is also the target of ketamine and its derivatives.

"That receptor is very well known to be associated with memory, learning, chronic pain, neurodegeneration," explains Riedel. "When that mechanistic approach was applied to MDD [major depressive disorder] with rapastinel, we saw very striking recovery in patients in a Phase 2a study, as well as a Phase 2b study. This became the foundation on which Allergan acquired rapastinel."

These other impacts are why Aptinyx continues to explore the NMDA receptor as a therapeutic target for chronic pain, PTSD and cognitive impairment in Parkinson's disease.

Riedel suggests that this allows the company to take a more holistic approach to the various comorbidities that overlap between the many disorders.

"They are always multifactorial diseases," he says. "None of them are just one thing only."

The early success of rapastinel hit a bit of a bump in March, however, with an announcement from Allergan, bringing into question rapastinel's development as adjunctive to antidepressant therapy for MDD.

In three acute studies, rapastinel did not differentiate itself from placebo on primary and key secondary endpoints.

"We are deeply disappointed with these results, and they are a vivid reminder that drug development is extremely challenging, especially in mental health," said Allergan's chief R&D officer, David Nicholson, in an announcement. "We will evaluate the impact of these data on the ongoing monotherapy MDD program and [Phase 2] suicidality in MDD study. We expect to make a decision on these programs during the course of 2019."

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CREDIT: BRAIN AND COGNITION DISCOVERY FOUNDATION

"Inflammation plays multiple roles involved in plasticity, regulating other neurochemistries like dopamine and serotonin, and having its own direct effect on brain systems relevant to the symptoms that we see in depression," notes Roger McIntyre, executive director of the Brain and Cognition Discovery Foundation.

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March was a good month for Sage Therapeutics and Janssen, however, as both companies saw FDA approval of their lead products in depression.

In a Phase 3 program, Janssen's nasal esketamine formulation (Spravato) was found to be superior to placebo when given on top of an oral antidepressant, providing significant improvement in symptoms of treatment-resistant depression. And in long-term studies, esketamine patients who achieved remission were 51 percent less likely to suffer a relapse than placebo patients.

Because esketamine is a derivative of illicit street drug ketamine, precautions are being taken with dosing such that patients will not take the drug home, but rather self-administer under clinical supervision.

Like rapastinel, esketamine targets the NMDA receptor, but rather than modulate activity, it completely blocks receptor function. This may help facilitate the rapid efficacy for which the drug has become known, but as Aptinyx' Riedel explains, it may also bring a lot of safety concerns.

"In oncology," Riedel continues, "when you have molecule go out of control—like a tyrosine kinase, for example—the goal has to be to shut that molecule down, to block it completely."

In the brain, however, the NMDA receptor is a very important player in normal brain physiology and is involved in a variety of neurological conditions, such as pain, PTSD and cognitive impairment.

"The idea of using a sledgehammer to shut that receptor off, in my view, is highly unphysiological," Riedel offers.

"The right approach is to ask has that receptor gone off-track a little and can you put it back on track by modulating it like a dimmer switch, as opposed to an on-off switch," he presses. "That, we have shown repeatedly and across multiple indications, gives you a much better efficacy and a remarkably better safety profile."

Within two weeks of the esketamine announcement, the FDA then announced approval of brexanolone (Zulresso) from Sage Therapeutics for the treatment of postpartum depression, the first and only such treatment.

A derivative of the naturally occurring progesterone metabolite allopregnanolone, brexanolone is an allosteric modulator of both synaptic and extrasynaptic GABAA receptors. In its three clinical trials, the drug achieved significant mean reductions in Hamilton Rating Scale for Depression (HAMD) total scores from baseline vs. placebo. Symptom reduction was seen as early as 24 hours, and could be maintained for up to 30 days.

"The potential to rapidly reduce symptoms in this critical disorder is an exciting milestone in women's mental health," offered clinical trial lead Samantha Meltzer Brody, director of perinatal psychiatry at UNC's Center for Women's Mood Disorders. "[Postpartum depression] is recognized to have significant and long-term impact on women and their families, but with Zulresso, we may finally have the opportunity to change that."

As McIntyre suggested above, however, there are numerous other areas being explored to understand depression pathophysiology and treatment, including inflammatory pathways.

Early this year, for example, Lisa Kalynchuk and colleagues at University of Victoria and University of Saskatchewan reviewed the evidence for antidepressant mechanisms of TNF-α antagonists.

"Treatment with proinflammatory cytokines, including IL-1, IL-6 or TNF-α, or lipopolysaccharide (LPS), induces sickness behavior and corresponding depression-like behavior on the forced swim test," they wrote. "Mice that lack certain cytokines or cytokine receptors do not display stress-induced depression-like behavior, which suggests that lower levels of cytokines confer a protective effect on the development of depression-like behavior."

The authors then highlighted evidence from several studies of patients being treated for autoimmune disorders with different TNF-α inhibitors.

"Patients with rheumatoid arthritis and plaque psoriasis taking prescribed etanercept, which is a TNF-α antagonist, reported significant reductions in depressive symptoms," they noted. "Similarly, patients with Crohn's disease receiving infusions of infliximab experienced significant reductions in depressive symptoms, and this decrease was associated with corresponding reductions in proinflammatory cytokines. Finally, psoriasis patients with comorbid psychiatric conditions report improvement in mood and overall well-being when taking infliximab."

Because etanercept does not cross the blood-brain barrier, the authors could not identify the mechanisms by which the anti-TNFs addressed depression, although they speculated that in binding peripheral TNF-α, it may promote activation of microglia, which results in decreased central secretion of TNF-α.

Jumping off findings like these, McIntyre initiated his own studies directly linking anti-TNFs and depression.

"I have a study that's in-press in *JAMA* where we gave patients infliximab as a treatment of their depression," he recounts. "We found that people who've had depression, who told us that they had trauma in their history, had a significantly greater improvement on the infliximab than they did with placebo."

Perhaps not surprisingly, even the microbiome is being explored as a possible entry point to understanding depression and response to treatment.

In January, for example, Tonji Medical Hospital's Chun Yang and colleagues examined the role of gut microbiota on the antidepressant effects of ketamine in an LPS-induced mouse model of depression. They noted that 30 bacterial species were significantly altered in prevalence between mice treated with LPS alone versus those treated with LPS plus ketamine.

In particular, the presence of two bacteria—the phylum *Actinobacteria* and the class *Coriobacteriia*—correlated with immobility time in a forced swim test, a test of stress meant to parallel depression in mice. To the authors, this suggested these microbes had potential as biomarkers of ketamine effectiveness.

Working in humans rather than mice, McIntyre looked for bacterial signatures or enterotypes in the feces of people with depression that differed from those found in healthy controls. And indeed, he found significant differences, particularly in the microbial diversity.

Thus, he says, "we wonder whether for some people, the altered inflammatory burden that we observe in depression—which, by the way is observed in 35 to 50 percent of patients—may have some type of contribution from the gut biome."

Despite these extended avenues of exploration, however, many challenges remain in the understanding of depressive pathophysiology and the ability to test new therapeutic candidates in a meaningful way. Part of that challenge is a lack of quantifiable markers of disease status and the largely subjective endpoints commonly used to diagnose patients and monitor response to treatment.

Begging for biomarkers

According to PPD's Peroutka, subjective endpoints are problematic, pointing to pain as the simplest example.

"We ask patients, zero to 10, what's your pain like?" he explains. "And what is a five to me versus you versus another person—we don't know that they're the same; there's no way to check that."

With depression, that uncertainty is amplified dramatically.

"Primary endpoint for HAMD is depressed mood: zero to four scale, how are we, no depression to severe depression," he says, adding that is just the first of 17 questions.

DRUGS IN DEVELOPMENT

COMPOUND	TARGET/MECHANISM	COMPANY
AGN-241751	NMDAR modulator	Allergan
ALKS-5461 (buprenorphine/samidorphan)	K-opioid receptor antagonist	Alkermes
AV-101	NMDAR antagonist	VistaGen Therapeutics
BLI-1005	Norepinephrine reuptake inhibitor	BioLite
Brexanolone (SAGE-547)	$GABA_A$ receptor positive allosteric modulator	Sage Therapeutics
Brilaroxazine (RP-5063)	$D_{2/3/4}$ receptor partial agonist 5-$HT_{1A/2A}$ receptor partial agonist	Reviva Pharmaceuticals
BTRX-246040	K-opioid receptor antagonist	BlackThorn Therapeutics
Cariprazine	Dopamine D_3 partial agonist 5-HT_{1A} partial agonist	Allergan
CERC-301	NMDAR antagonist	Cerecor
CERC-501	K-opioid receptor antagonist	Janssen
Dextromethadone (REL-1017)	NMDAR antagonist	Relmada Therapeutics
Esketamine	NMDAR antagonist	Janssen
FKB01MD	5-$HT_{1A/1D}$ receptor agonist Serotonin reuptake inhibitor	Fabre-Kramer
ITI-007	5-HT_{2A} receptor antagonist	Intra-Cellular Therapies
MIN-117	5-$HT_{1A/2A}$ receptor antagonist Serotonin/dopamine reuptake inhibitor	Minerva Neurosciences
Minocycline	Antibiotic Anti-inflammatory?	
Nitrous oxide	NMDAR antagonist	
NRX-100/NRX-101 (ketamine + cycloserine/lurasidone)	NMDAR antagonist (ketamine) NMDAR modulator (cycloserine) 5-HT_{2A} receptor antagonist (lurasidone)	NeuroRX
PH 10	Pherine neurosteroid	VistaGen Therapeutics
Pimavanserin	Selective serotonin inverse agonist	Acadia Pharmaceuticals
Rapastinel	NMDAR partial agonist	Allergan
S-47445	AMPA positive allosteric modulator	Servier
SAGE-217	$GABA_A$ receptor positive allosteric modulator	Sage Therapeutics

SEARCHING EVERY HAYSTACK: A partial list of some of the drugs and their targets in development for bipolar depression, major depressive disorder, post-partum depression and treatment-resistant depression.

Feelings of guilt, zero to four, he recounts. Suicidal thoughts, zero to four. Insomnia, early at night…the questions and scales keep coming.

He quickly notes that he is not arguing the tests are spurious—HAMD and its ilk have been validated.

"But along all those different scales, you can see the challenge is that it's just too subjective," he says.

And even if you could convince yourself that one patient's score in one category is every other patient's score in the same category, there is the broader question of the continuum of scores.

"Is a 15 depression score different than a 25?" Peroutka asks. "The answer is yes. But in clinical trials, we lump all of them together."

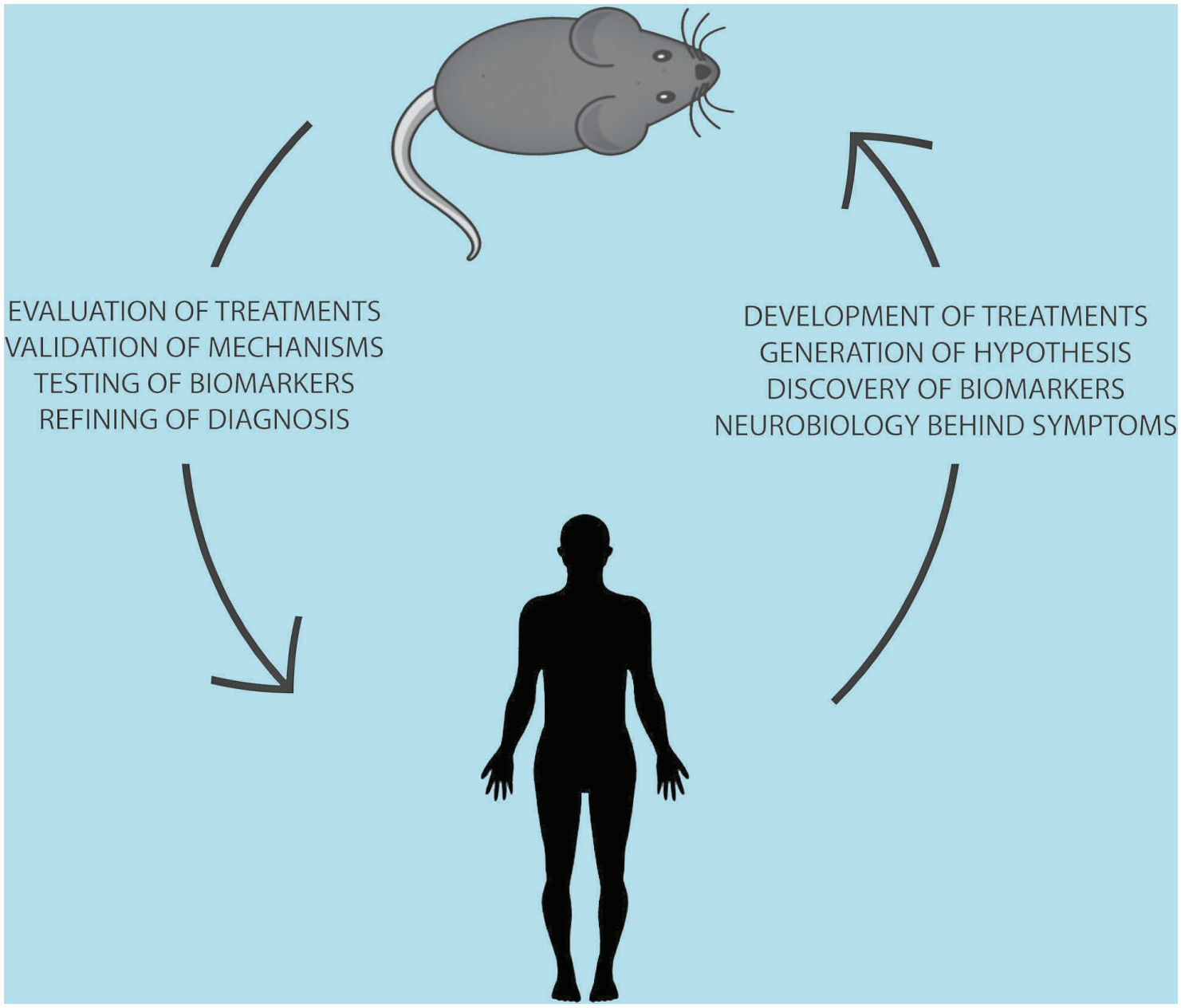
To get more meaningful data in a clinical trial, he suggests, it might be preferential to narrow the range of subjects as a statistical way of homogenizing the patient population.

A molecular biomarker or panel might clarify some of this uncertainty, but finding one has proven elusive.

"I don't think we have a really good handle on the underlying molecular pathology of defined depressive disorder," explains Riedel. "It is a very complex disease and varies as to which pathology matters to which patient or another—similar, I think, to the example in oncology where not every tumor is the same."

Efforts have been made to identify biomarkers, he continues, and these efforts have met with limited success, in that researchers have managed to make only modest correlations between a particular biomarker and the disease. He questions, however, whether those correlations have been consistent enough to offer any predictive value.

"There is a prevailing view that if we ever have such a thing," McIntyre adds, "it's going to be exceptionally complicated because of the complexities of the biology."



FRUITFUL FEEDBACK. It is possible that for animal models of depression to improve, they must not only feed the clinical experience, but also be fed by it. (Adapted from Söderlund, Lindskog. *Int J Neuropsycho.* 2018:21;668-676.)

CREDIT: APTINYX

"The idea of using a sledgehammer to shut [the NMDA] receptor off, in my view, is highly unphysiological," says Norbert Riedel, president and CEO of Aptinyx. "The right approach is to ask has that receptor gone off-track a little and can you put it back on track by modulating it like a dimmer switch, as opposed to an on-off switch. That, we have shown repeatedly and across multiple indications, gives you a much better efficacy and a remarkably better safety profile."

"Part of the challenge we have is that because we don't have a blood test or chest X-ray or CT scan to make the diagnosis, we rely on symptom ratings," he presses. "We rely on clinician impressions, and they are far from perfect.

"They're not useless—that's what we base our whole careers on—but they're not perfect. And that introduces, as you might expect, variability."

That variance makes it very difficult to achieve any consensus, McIntyre adds, because clinicians and researchers can't even agree on what the phenotype is.

"In cancer, they agree that there's the tumor," he offers as an example. "In heart disease, they agree you've had a heart attack. This is something we agree on.

"But the challenge is that we just can't agree on what the lesion looks like in depression, which makes the search for a biomarker to make the diagnosis not believable at this point in time."

Peroutka sees a strong parallel between today's analysis of depression and that of multiple sclerosis 25 years ago.

"MS was defined as two separate neurological lesions or deficits in space and time," he explains. "So, if I was to ask you has your left or right foot fallen asleep in the last year, and you'd probably say yes. I'd then ask did your opposite hand or fingers ever fall asleep in the past year, and you'd probably say yes. Technically, you could be diagnosed 25 years ago with MS."

Now, with MRI-based brain scans, he says, it really doesn't matter how the patient answers questions or even why the patient has come in for the scan.

"If you're scanned for a neck injury, and you have plaques in your head, then you have MS," he adds.

The desire for and potential of recognized biomarkers has led to several labs approaching the problem from a multitude of directions.

Earlier this year, for example, Peng Xie and colleagues at Chongqing Medical University described their efforts to identify metabolite signatures in the urine of patients experiencing depressive episodes in bipolar disorder (BD).

"A clinical review recommended that the antidepressants should be stopped in period of mania, and the antidepressants should be used with a mood stabilizer in period of depression," the authors explained. "Given these facts, there is an urgent need to develop objective diagnostic methods for BD patients during different episodes."

In considering their approach, the researchers suggested that no single methodology would give the wide coverage or meaningful results they would need, so they opted for a dual-platform approach using GC-MS and NMR spectrometry to profile urine from young and middle-aged subjects.

Comparing samples from healthy controls and affected patients, the scientists identified 13 differentially regulated metabolites, most of which were involved in carbohydrate and energy metabolism. Of these, they defined a biomarker panel of five metabolites that they suggested could be helpful in developing an objective diagnostic method.

"A previous study reported that the brain energy metabolism in BD patients was altered," they stated, finding their results consistent with others. "Our previous studies have also identified some differential urinary metabolites that were involved in energy metabolism in depressed patients. Meanwhile, we also observed the perturbed energy metabolism in the cerebellum of chronic mild stress-treated depressed rats.

"Based on these results, we deduced that the pathogenesis of BD might be associated with the disturbance of energy homeostasis that was caused by the dysfunctional [hypothalamic-pituitary-adrenal] axis."

In a similar effort also reported this year, Daihui Peng and colleagues at Shanghai Jiao Tong University & Deakin University used UPLC-3Q-MS to examine blood samples from healthy controls and subjects with MDD or bipolar

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disorder. Specifically, they wanted to identify any correlations between metabolites in the kynurenine pathway (KP) and depression presence and severity, as determined with the HAMD-24 survey.

Part of the attraction for KP in particular is a growing understanding of its possible role in a number of neurological disorders, including depression.

"Myint and Kim's widely accepted 'KP metabolic imbalance hypothesis' proposes that metabolic imbalance is the major mechanism of KP-induced depression," the authors noted. "In line with this, variations in metabolic factors in the KP and relevant enzymes have been found in MDD, bipolar affective disorder and several neurodegenerative diseases."

The researchers identified several metabolites that were differentially expressed between healthy controls and depressed subjects, although they noted no significant differences between subjects with MDD or bipolar disorder.

As well, there was an inverse correlation between the severity of depression and metabolite levels; for example, lower levels of tryptophan and kynurerine were associated with more severe symptoms. And although not perfect, there was a strong indication that many of these levels could be used for clinical diagnosis.

"The associations between HAMD-24 scores and metabolic factors in MDD suggest variations in [tryptophan] exert a critical role in disease remission," the authors concluded. "Most importantly, [kynurenic acid] is a potential biomarker discriminating MDD and healthy controls, offering a novel diagnostic method for clinicians."

Glen Baker and colleagues at the University of Alberta, meanwhile, recently reviewed efforts to understand the roles of D-serine in both schizophrenia and depression. Beyond the compound's potential as an NMDA receptor co-agonist, the researchers suggested it has also shown potential as a predictive biomarker for antidepressant response to ketamine.

"Several interesting pharmacodynamic and pharmacokinetic interactions between D-serine and ketamine have been reported, and, interestingly, evidence suggests that low plasma levels of D-serine may predict positive antidepressant response to ketamine," the authors summarized. "Several animal model and clinical studies also indicate that D-serine may be effective in reducing cognitive deficits, but that further study is necessary before considering it an effective cognitive enhancer for routine use in humans."

Whether looking at metabolite panels, cytokine levels or protein markers, however, there is still a significant gap between experimental correlations and validated, broadly accepted biomarker.

In fact, Riedel is not completely sure that the FDA is ready to immediately accept an objective biomarker that correlates with disease.

"Even if we had [a good biomarker] and we could show that it can be changed with a drug, the FDA would say that's not good enough, I still need to have patient-reported or physician-reported subjective methods of verification," he suggests. "The biomarker may be supportive, but it will not become the endpoint upon which you decide the drug gets regulatory approval. We are a long distance from that."

And until biomarkers are accepted as objective endpoints, studies of depression will continue to struggle with another major obstacle: the placebo effect.

Because diagnostic panels like HAMD rely on patient-reported feedback—Do I feel better? Do I feel less depressed?—many clinical studies can suffer from a very strong placebo response, says Riedel.

In part, according to Peroutka, it is the nature of the disorder.

It's the natural history of the disorder that people get better on their own, he says. Depression is episodic, by definition in the case of bipolar disorder, and so even without therapeutic intervention, a percentage of patients in a clinical trial may feel better.

This sets an artificially high bar over which any study treatment must show an effect.

Riedel also offers the example of functional unblinding of the study, where patients and clinicians know whether the patient is receiving the study drug vs. placebo because of the associated side effects.

Thus, a positive response may have little to do with drug efficacy but rather the awareness of treatment and the belief that it will have a positive impact.

"We probably leave a lot of good compounds behind because they really can't overcome the placebo effect even if they are perfectly active drugs," Riedel says.

"There may have to be different thinking about how we design and execute trials," he continues. "Maybe we measure the activity of a drug against the baseline that is known in each of these patients."

Long before any candidate reaches clinical trials, though, the search for effective and safe antidepressants is also challenged by the models on which these drug leads are initially tested.

Middling models

Another issue of using subjective, query-based diagnostics criteria such as the HAMD is that unlike molecular biomarkers, which may also be found in model organisms or have analogues, it is difficult to find a rat, mouse or non-human primate that can directly answer questions about how depressed they are feeling.

"In mood disorders like depression, it is hard to measure depression in a rodent," acknowledges Riedel. "There are ways in which we look at this, but I would say that it is of limited value in predicting a human disease course in a depressive disorder."

"There is no question that the animal models we have are not just imperfect, but are serving as a major limitation to progress in the field," McIntyre adds.

In place of the HAMD, researchers are forced to use stress- and anxiety-inducing tests on lab animals, such as the forced swim test mentioned earlier or the tail suspension test. Another commonly used test is a measure of anhedonia—losing the ability to derive pleasure from something that usually produces pleasure. In the case of rodents, this is often measured in the preference for sweetened over unsweetened water.

But how well does the rodent response reflect the human condition?

"I have done that forced swim test [on rodents]," offers Riedel. "Why would you stop swimming? Well, maybe the rat doesn't know how to swim. Maybe it's weak. Maybe it did well the day before."

"But to say that it is because they're depressed is a stretch," he adds,

In a recent review, Karolinska Institutet's Johan Söderlund and Maria Lindskog chose to see these tests in a different light.

"When we compare animal models with clinical conditions, we need to use less well-established clinical descriptions," they opined. "These conditions are often associated with an increased risk of developing major depression, but are not major depression per se."

"It becomes clear that the animal models are not diagnostic models, but rather models of risk and vulnerability factors of depression," they continued. "Importantly, this is not a drawback of the animal models, but again illustrates that the current diagnostic system is neither compatible with neuroscience nor is it sufficient to describe the underlying mechanisms of depression."

And just as the array of approaches to depression pathophysiology has expanded in human profiling, the pair noted that this is also the case in animal model development, suggesting that we are moving well beyond simply behavioral assays and into more molecular modalities such as gene knockouts, optogenetic stimulation and neuroinflammatory models.

McIntyre also sees hope in efforts to model depressive disorders using stem cell approaches.

"If you can take a stem cell from someone who has been affected by depression and induce it into a neuron, what you've effectively done is you've put into your dish a neuron which presumably is identical to the neuron in the brain," he says, acknowledging that this is yet a work in progress. "But you can imagine that this is a better methodology than the animal models."

Indeed, companies like StemonX and Stem Cell Technologies, as well as organizations like the Wyss Institute, have put a lot of effort into the development of brain cell organoids and spheroids, as well as brains-on-a-chip and blood-brain barrier mimics to offer researchers everything from precision medicine approaches to specific patients or simply deeper molecular understandings of cell communication and drug pharmacology.

But if we thought it was difficult to ask a mouse how it felt, we can only imagine the effort to do so with a microwell of cells, no matter how well-organized.

For Söderlund and Lindskog, animal models and human experience can only improve by taking a feedback approach.

"Clinical experience is necessary to develop fruitful animal models, but the animal models are also needed to delineate the complex patterns of different exposures and vulnerability factors characterizing the clinical situation, indicating the potential mutual benefit between research and clinic," they concluded.

As the repertoire of possible treatments slowly expands, perhaps a similar feedback loop needs to tighten between patients and clinicians, clinicians and researchers, and patients and communities. ■

EDITCONNECT: E041931

Metabolism and mood

As recent efforts to study the gut-brain axis with microbiomics or correlations between metabolic syndrome and the onset of neurodegenerative diseases like Alzheimer's would indicate, there is a slowly growing awareness of links between metabolism and mood disorders like depression.

As the University of Toronto and University Health Network's Roger McIntyre explains, although insulin is prevalent in the brain, it is not being utilized for glucose homeostasis as it is elsewhere in the body.

"The evidence indicates that insulin is a brain peptide that serves a tropic role," explains McIntyre, who is also executive director of the Brain and Cognition Discovery Foundation. "It's responsible for neurodifferentiation, neuroplasticity and also reducing apoptosis."

And just as too much or too little insulin is problematic in the periphery, so too does the imbalance create problems in the brain.

"If your brain is exposed for a significant period of time to elevated levels of insulin—which is seen in early type 2 diabetes—that can set in motion, in the short term, something you don't want," he continues. "What happens is that the brain begins to deposit amyloid, the protein implicated in Alzheimer's disease."

This happens because insulin uses the same degradation pathway as amyloid. Thus, when there is a relative excess of insulin, it is preferentially degraded, leaving amyloid to build up and then triggering an inflammatory cascade.

"Diabetics have very high rates of Alzheimer's disease," McIntyre adds. "It is now said that 10 to 15 percent of all AD cases are directly due to diabetes."

But how does this impact depression?

According to McIntyre, upward of 30 to 40 percent of people with depression—including those without diabetes—exhibit impaired insulin-glucose homeostasis.

Thus, he continues, "because people with diabetes and depression have hyperinsulinemia for a long time, the amount of insulin getting into your brain over time begins to diminish. The brain adapts, it decreases the insulin uptake."

"And the problem with diminishing insulin uptake in response to peripheral hyperinsulinemia is that now you're losing those key roles that insulin performs in your brain: neurodifferentiation, neuroplasticity, as well as inhibiting apoptosis," he says, bringing the discussion full circle.

It's a double hit, he remarks.

"In the short-term, you get this amyloid deposition. And in the long-term, you lose the tropic support."

Given this paradigm, McIntyre and colleagues have examined the impact of the GLP-1 receptor agonist liraglutide on non-diabetic subjects experiencing depression. In a pilot study, they found that a four-week regimen was not only safe and well tolerated, but also subjects showed significant improvements in cognitive function.

Similar effects have been seen with other diabetes therapies, including metformin, offering another avenue of antidepressant exploration. ■