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Is It Time to Rethink How We Support Depression Management?

**Announcer:**
You're listening to *Psychiatry Today* on ReachMD.

This medical industry feature, titled "Is It Time to Rethink How We Support Depression Management?" is sponsored by Alfasigma.

Here's your host, Dr. Charles Turck.

**Dr. Turck:**
Welcome to *Psychiatry Today* on ReachMD. I'm Dr. Charles Turck.

Today, I'm speaking with Dr. Andrew Cutler and Dr. Gus Alva about a broader biologic perspective on depression—specifically, how recognizing multi-system contributors can help us build a more supportive foundation for depression care.

**Dr. Turck:**
Dr. Cutler is a psychiatrist and serves as Chief Medical Officer at the Neuroscience Education Institute in Malvern, Pennsylvania. He's also a Clinical Professor in the Department of Psychiatry and Behavioral Sciences at State University of New York Upstate Medical University in Syracuse.

Dr. Cutler, welcome to the program.

**Dr. Cutler:**
Thanks for having me, Charles.

**Dr. Turck:**
Also with us is Dr. Alva. He's a psychiatrist and a Distinguished Fellow of the American Psychiatric Association. He also serves as Medical Director of ATP Clinical Research in Orange County, California, and previously served as Deputy Director of clinical research and as an Associate Professor in the Department of Psychiatry and Human Behavior at the University of California, Irvine.

Dr. Alva, thanks for joining us today.

**Dr. Alva:**
It's great to be here, Charles.

**Dr. Turck:**
Well, let's dive right in. We know depression is prevalent—data suggests around 21 million adults and five million adolescents in the US experience major depressive episodes.[1] But despite the treatments we have, remission remains a real challenge. With that being said, Dr. Cutler, what are your thoughts on where we currently stand when it comes to the management of depression?

**Dr. Cutler:**
Well, you're right, Dr. Turck, the numbers are staggering, and beyond the core symptoms of depression, the impact on quality of life can be profound, because depression affects emotional regulation, cognition, productivity, and overall functioning.[1-3]

And we've seen that less than half of patients respond to first-line antidepressants, and unfortunately, response rates actually decrease with every additional change in therapy.[4] And so, we have up to 70 percent of patients failing to achieve remission which is our goal with our first antidepressant.[5] Now this trial-and-error process can be difficult for both clinicians and patients.[4] And it really highlights

that for a majority of our patients, the current approach isn't fully meeting their needs.

**Dr. Turck:**
Now it's clearly a really tough reality out there. And turning to you now, Dr. Alva, what are some factors that may contribute to this gap?

**Dr. Alva:**
Well I think, in part, we may not be addressing the full underlying pathology around depression. Our current treatment options often target serotonin and norepinephrine with selective serotonin reuptake inhibitors, or SSRIs, and serotonin norepinephrine reuptake inhibitors, or SNRIs.[6] But a growing body of research shows that depression is a multifactorial condition and isn't necessarily driven by monoamines alone.[7-15]

A broad range of imbalances across multiple biological systems can contribute to its pathology. For example, other neurotransmitters that play key roles in regulating depression include dopamine, glutamate, and GABA.[8]

And beyond neurotransmitter synthesis and metabolism, factors such as hypothalamic-pituitary-adrenal axis or—HPA—dysregulation, neuroinflammation, and oxidative stress can affect these signaling pathways.[11,16-19] So I think a broader understanding of these underlying contributors also means a broader approach to targeting them.

**Dr. Turck:**
Well, let's dig into that, Dr. Alva. Would you tell us more about how other signal pathways fit into the broader picture?

**Dr. Alva:**
Absolutely. To give you an example, an imbalance between glutamate and GABA activity can lead to excitotoxicity, which contributes to neuronal injury and disrupts normal neurotransmission.[10,12] And increased inflammatory cytokines or reactive oxygen species can contribute to neurotoxicity.[11] As I mentioned, elevated cortisol levels from HPA axis dysregulation are also associated with depression, so these pathways are complex and interconnected.[17]

Think of it as a cycle, where oxidative stress can deplete the very nutrients needed to synthesize neurotransmitters, which then exacerbates their imbalance.[19] So, disruptions in one pathway—whether it's oxidative stress, inflammation, or glutamate modulation—can affect the others. That's why we really need to think about restoring balance across the full neurobiological network, beyond targeting monoamine levels.

**Dr. Turck:**
So, we've talked about imbalances in neurotransmitters, inflammation, oxidative stress, and the HPA axis—let's come back to you now, Dr. Cutler. How do nutrient deficiencies factor into these imbalances?

**Dr. Cutler:**
Well, biochemical processes require a sufficient level of key nutrients to function.[20] And specific nutrient deficiencies are quite common in people with depression—things like folate, vitamin D, and zinc.[21-23] Now, what we're learning is that some nutrient deficiencies can actually alter how antidepressants are metabolized. And this can lead to two major problems: a reduction in the therapeutic effect of the drug, or an increase in the risk of side effects.[20]

So, to take a step back, we have to consider *why* these deficiencies are happening. Now diet plays a role, but many other factors can also lead to nutrient deficiencies. Chronic stress, for instance, increases the metabolic demand for these nutrients—essentially, the body "burns through" its reserves faster to manage the stress response.[24,25] And medications like metformin or oral contraceptives can also deplete them over time.[26,27] And even aging affects absorption. So, if we want to build a stronger biological foundation to support an effective treatment response in depression, we have to consider additional underlying factors, including patient characteristics and lifestyle factors that may increase demand for these nutrients.

**Dr. Turck:**
For those just tuning in, you're listening to *Psychiatry Today* on ReachMD.

I'm Dr. Charles Turck, and today I'm speaking with Dr. Andrew Cutler and Dr. Gus Alva about understanding depression as a multi-system condition and the role of targeted medical nutrition in clinical management.

**Dr. Turck:**
Now, Dr. Cutler, we've discussed the need for a broader approach, so let's talk about how we might translate that knowledge into clinical practice. What approaches are available to help our patients build a strong biological foundation?

**Dr. Cutler:**
Well, of course, in addition to diet and lifestyle interventions, one example is DeplinPRO Mood Health™, which is a medical food specially formulated to help meet the distinct nutritional requirements for neurotransmitter imbalances in the clinical dietary management of mood disorders, including depression. It's intended for patients aged twelve years and older, not just 18, and is to be used under medical supervision once daily in combination with an antidepressant.

It combines four nutrients: 15 milligrams of L-methylfolate calcium, 25 milligrams of zinc, 50 micrograms—or 2000 International Units—of vitamin $D_3$, and 250 milligrams of L-theanine.

The formulation reflects nutrients studied in relation to key factors of depression management such as: mood regulation,[9-12,28] neuroprotection,[10-15,29] mental resilience,[13,15,30] stress management,[9,13,15] and cognitive function.[11,12,15,31]

Now it doesn't replace pharmacologic therapy. It's designed to support neurotransmission and provide that biological foundation we discussed, so that any treatment the patient is on can work as intended.

Now, if we think back to the pathways that Gus so well just elaborated, monoamine neurotransmission, oxidative stress, inflammation, HPA axis dysregulation, glutamate imbalance—all of these systems rely on nutrient-dependent biochemical processes.[11,16-19] They don't function in isolation, and they don't function optimally without the right substrates and cofactors in place.[20]

And the nutrients in DeplinPRO Mood Health target these pathways.

L-methylfolate, zinc, and vitamin $D_3$ support monoamine neurotransmission by helping synthesize serotonin, dopamine, and norepinephrine and maintain glutamate balance.[10-12,28,32] Together with L-theanine, they also may play roles in modulating inflammatory and oxidative stress responses while supporting neuroplasticity.[10-15,29,33-35]

Zinc, vitamin $D_3$, and L-theanine contribute to stress-response modulation—particularly through effects on the HPA axis and cortisol regulation—while also supporting neural communication and plasticity.[10,14,33,36]

So what you see here is an overlap. Each ingredient doesn't just target one pathway; there's cross-talk. And that's important, because depression itself isn't driven by a single disrupted mechanism. It's a network condition.[20]

**Dr. Turck:**
Now, with that background in mind, Dr. Alva, would you walk us through the clinical evidence for these specific ingredients?

**Dr. Alva:**
I'd be happy to. Let's start with the L-methylfolate, because that's where we have an example of augmentation data in a defined population.

There was a randomized, double-blind, multicenter trial that looked at patients with major depressive disorder who had a partial or no response to a selective serotonin reuptake inhibitor. Patients were randomized to receive either placebo or 15 milligrams of L-methylfolate in addition to their SSRI.[37]

Looking at the Phase two portion, 32.3 percent of patients receiving L-methylfolate plus the SSRI met response criteria, compared with 13.6 percent of those on SSRI plus placebo. That difference was statistically significant, P equaling 0.04. So you're talking about twice as many patients responding when L-methylfolate was added.[37]

And symptom severity moved as well. There was an 84 percent greater improvement in Hamilton Depression Rating Scale scores with L-methylfolate plus SSRI compared with SSRI alone. That mean change was minus 5.6 versus minus 3.0, with a P equaling 0.05.[37]

Now, it's still important to keep it grounded—this was a specific group: patients who hadn't had an adequate response to medication alone. So I don't take that and generalize it to every patient with depression. But it does show statistically significant improvement in that setting, which is clinically meaningful for the types of patients we're often trying to help.

And what's also encouraging is that 61 percent of patients achieved remission at month 12, which suggests potential for sustained improvement.[38]

When it comes to safety, L-methylfolate was generally well tolerated, with an adverse event frequency similar to placebo. There were no significant differences in change in weight, heart rate, or blood pressure between groups, and there was also no significant sexual dysfunction reported in those receiving L-methylfolate.[37]

**Dr. Turck:**
And Dr. Cutler, would you expand on the other ingredients mentioned, like zinc and vitamin D?

**Dr. Cutler:**
Well, sure thing—there's data there as well. In addition to the really excellent data that Gus just went over with us.

One example is a 12-week, double-blind, randomized, placebo-controlled trial in individuals who were overweight or obese. They looked at zinc at 30 milligrams per day, vitamin $D_3$ at 2000 international units per day, and then the combination, versus placebo. They measured depression symptoms using a standard scale called the Beck Depression Inventory-II.[39]

At 12 weeks, the combination group had a mean change of minus 7.62. Zinc alone was minus 7.02, vitamin D alone was minus 3.87, and placebo was just minus 0.76. So the difference for the combination versus placebo was statistically significant, with a P value of less than 0.0001.[39]

Interestingly, they also reported a decreasing trend in cortisol in the combination group, which may suggest a role in stress-response modulation, but keep in mind that those findings were exploratory.[39]

Now in terms of safety, they didn't see evidence of negative side effects across the groups receiving zinc, vitamin $D_3$, or the combination. And no serious adverse events were observed. So overall, the studies we're discussing suggest these ingredients were generally safe and well tolerated in those trial settings.[39]

**Dr. Turck:**
Thanks for that rundown and turning to you now, Dr. Alva, when you think about targeted medical nutrition in depression management, what types of patients come to mind as the best candidates?

**Dr. Alva:**
That's a great question. I tend to think about patients in my clinic who have had a partial response to SSRIs and SNRIs or those for whom we'd want to consider the broader clinical picture.[37,40]

That might include individuals with medical comorbidities such as diabetes or known genetic variations, such as *MTHFR,* or who have limited sunlight exposure or are on certain medications, such as oral contraceptives, as these can all influence nutrient status over time.[24-27,40-44]

In short, I'm thinking about patients whose nutritional needs aren't being met through diet alone—especially when dietary changes by themselves aren't practical or sufficient to close those gaps. It comes down to identifying patients who may benefit from targeted medical nutrition as part of their overall treatment approach.

So it's not one specific patient profile. It's more about recognizing that nutrient imbalances or increased demands of specific nutrients could be part of the overall clinical picture.

**Dr. Turck:**
Before we wrap up our program, Dr. Alva, what are some practical takeaways for our listeners regarding targeted medical nutritional support?

**Dr. Alva:**
First, depression is biologically complex. Monoamine signaling remains central, but it operates within a broader network of underlying pathologic mechanisms.[8] And certain nutrients—including L-methylfolate, vitamin $D_3$, and zinc—are frequently found to be deficient in individuals with depression.[20-23] So as our understanding of depression biology expands, it's important to consider a more comprehensive approach, such as targeted medical nutritional support.

DeplinPRO Mood Health is one example, intended for use under medical supervision alongside an antidepressant medication in adults and, as Andy made mention, adolescents age 12 years and older.

It's formulated with L-methylfolate, vitamin $D_3$, and zinc— nutrients that have been studied in relation to pathways involved in depression biology, and that are generally well tolerated in the populations evaluated.[37-39]

For patients who continue to struggle with incomplete response, expanding our lens to include underlying biologic and nutritional factors may be another way to support their care.

**Dr. Turck:**

Thank you both—this was an informative discussion. And with those final thoughts in mind, I want to thank my guests, Dr. Andrew Cutler and Dr. Gus Alva, for breaking down our evolving understanding of depression biology and how it may inform clinical practice.

Dr. Cutler, Dr. Alva, it was great speaking with you both today.

**Dr. Cutler:**
Well, thanks so much, Charles. What a pleasure to be here, especially with my good friend Gus Alva, and I hope this information was helpful to our audience.

**Dr. Alva:**
I echo Andy's sentiments. I'm deeply honored to have been a part of this particular program. Charles, continue doing the great work that you're doing for our audience, and it's been a delight. Thank you.

**Dr. Turck:**
Thanks so much. For ReachMD, I'm Dr. Charles Turck. Thanks for listening.

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