This Academic Highlights section of *The Journal of Clinical Psychiatry* presents the highlights of the virtual roundtable "Patient Functioning and Life Engagement: Unmet Needs in MDD and Schizophrenia," which was held May 10, 2022.

The roundtable was chaired by **Christoph U. Correll, MD**, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, and Charité Universitätsmedizin, Berlin, Germany. The faculty were **Zahinoor Ismail, MD**, Department of Psychiatry, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada; **Roger S. McIntyre, MD**, Mood Disorder Psychopharmacology Unit, University Health Network, Department of Psychiatry, University of Toronto; Institute of Medical Science, University of Toronto; and Departments of Psychiatry and Pharmacology, University of Toronto, Toronto, Ontario, Canada; **Roueen Rafeyan, MD**, Department of Psychiatry, Feinberg School of Medicine, Northwestern University, Chicago, Illinois; and **Michael E. Thase, MD**, Department of Psychiatry, Perelman School of Medicine of the University of Pennsylvania, and the Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, Pennsylvania.

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Patient Functioning, Life Engagement, and Treatment Goals in Major Depressive Disorder

Christoph U. Correll, MD; Zahinoor Ismail, MD; Roger S. McIntyre, MD; Roueen Rafeyan, MD; and Michael E. Thase, MD

Outcome measures in major depressive disorder have traditionally focused on characteristic symptoms included in the *DSM-5*[1] definition of major depressive disorder (MDD): depressed mood, lack of interest or pleasure in activities, fatigue, guilt, and change in weight/appetite. Addressing these symptoms is clearly a treatment priority, especially in the acute stages of the treatment process. However, patients express that, beyond symptom relief, they have additional goals: restoration of functioning and of the feeling that one can participate in, and engage with, their own life. Life engagement encompasses aspects of life experience relating to cognition (including cognition colored by emotion), vitality, motivation and reward, and the ability to feel pleasure.[2]

In a recent roundtable meeting, a panel of 5 experts discussed life engagement and its relationship to symptoms and functioning in patients with major depressive disorder and schizophrenia. This Academic Highlights, part 3 in a series, summarizes the experts' discussion of how life engagement can be integrated into patient-centered discussions of treatment goals, as well as how it can inform treatment selection in for those with MDD.

INCORPORATING THE PATIENT'S PERSPECTIVE WHEN PLANNING TREATMENT

According to Dr McIntyre, clinicians should involve patients with MDD in the treatment planning process; first, because they *want* to be involved, and second, because the patient is the one living with the illness. The patient should be the one prioritizing the therapeutic objectives, and it is not for the clinician to impose their objectives on the person living with the condition. Dr Ismail agreed:

> It's always instructive, whether it be for MDD or schizophrenia, to get a sense of a person's treatment goals. It helps us to understand what they expect from treatment, and then we can consider whether these are realistic goals. In the context of treatment, I like to ask, What is someone doing? How do they like that? And what would they *like* to be doing?

Dr Thase pointed out that such discussions can provide valuable context regarding the patient's past level of engagement and functioning. Further, involving the patient in planning can augment the sense of agency that is often compromised in people with MDD. Shared decision making in patients with depression has been shown to improve treatment adherence and patient satisfaction, with no increase in consultation time.[3]

A survey of patients with MDD found that 42% had goals for treatment.[4] Frequently cited goals included aspects of life engagement such as cognitive function (60%), especially memory, and interpersonal aspects of life (57.8%), particularly social engagement. Dr McIntyre encouraged clinicians to set concrete SMART (*S*pecific, *M*easurable, *A*ttainable, *R*elevant, and *T*ime-bound) goals with their patients, saying that they "are time-savers, and they don't disappoint." He relayed that in his practice, such conversations have provided fertile ground to hear, in the patient's own language, what engagement means to them and how it fits into their objectives.

ASSESSING LIFE ENGAGEMENT IN PATIENTS WITH MDD

The movement in clinical research toward outcomes that focus on the patient's perspective has created a need for valid, reliable patient-reported outcome measures[5] that assess outcomes valued highly by patients, such as life engagement. Life engagement reflects an outcome that overlaps with, but is not fully captured by, other outcomes in mental health. It entails the improvement of anhedonia and apathy, but these alone do not fully capture aspects of life engagement relating to attention and alertness.[6,7] Likewise, quality of life measures do not capture the energy and alertness aspects of life engagement.[7] Dr Thase explained,

> Our patients have told us over and over that they want something more than relief of symptoms. We've found that it's not just functional recovery, but also a return to one's ability to engage in life. This engagement is multidimensional, but it gets at the essence of what makes life worth living. We had a hard time pinpointing this in our symptom scales because the symptom scales reflect illness and not wellness.

Dr Correll summarized the importance of developing a measure specific to life engagement: "We only recognize what we see, and we only see what we look for, and to look for something we need to conceptualize it." A systematic review[7] identified only 2 existing validated measures described by their authors as assessing life engagement: the Engaged Living Scale[8] and Life Engagement Test.[9] However, these scales do not capture all of the essential areas of life engagement according to a validated framework developed with expert psychiatrists and validated via interviews with patients with MDD.[6]

In the absence of a scale to assess life engagement in patients with MDD, an expert panel[10] selected 10 items that represent patient well-being and life engagement from the Inventory of Depressive Symptomatology Self-Report (IDS-SR),[11] a patient-reported outcome measure that evaluates core depressive symptoms and atypical and melancholic symptom features of MDD. The IDS-SR was included in the phase 3 randomized controlled trials of adjunctive brexpiprazole in MDD, and the expert panelists' selection of the life engagement items was inspired by feedback from patients who participated in those trials.[12–14] Items selected from the IDS-SR to represent life engagement are listed in Box 1.

To confirm that the 10 items in the IDS-SR_{10} Life Engagement subscale reflected patients' views of life engagement, and to support the use of the scale in clinical research, interviews were conducted of 20 patients with MDD.[15] They found life engagement, as described in the interview, to be an important outcome, and 19 of 20 agreed that all selected IDS-SR items were relevant to life engagement.

Dr McIntyre stated that a scale measuring life engagement should be sensitive to changes in illness severity and that the IDS-SR subscale accomplishes this. He noted that he includes measures of depression, anxiety, functioning, and engagement into his practice and that the IDS-SR_{10} subscale (as well as a life engagement subscale developed from the Positive and Negative Syndrome Scale for use in schizophrenia[16]) would be brief, actionable, and cost-efficient to implement at the point of care.

Box 1. IDS-SR Items Selected to Represent Life Engagement in Major Depressive Disorder[a]

1. Response of your mood to good or desired events
2. Concentration/decision making
3. View of myself
4. View of my future
5. General interest
6. Energy level
7. Capacity for pleasure or enjoyment (excluding sex)
8. Interest in sex
9. Feeling slowed down
10. Interpersonal sensitivity

[a]Based on Thase et al.[10]

Case Practice Question

Discussion of best response can be found at the end of the activity.

Elise is a 32-year-old single woman employed in the tech sector and working both at the office and from home in a hybrid schedule. She was diagnosed with MDD 4 years ago and initially treated with cognitive-behavioral therapy and an SSRI. Her depression has returned in the past 6 months, and Elise has re-initiated treatment with the SSRI that was effective during her index episode. She feels fatigued and apathetic and has been experiencing middle insomnia and moderate anxiety, with no suicidal ideation. Her Patient Health Questionnaire-9 score is 15, and her Generalized Anxiety Disorder-7 score is 8. Elise tells you, "The antidepressant is making me feel foggy. I feel I'm drugged." Previously, she enjoyed binge-watching shows on streaming services, but she finds herself no longer reacting even to her favorite dramas. Her concentration has diminished. Elise feels "disengaged" from herself, work, and friends and has had to take a few "mental health days." She has no other medical problems, and her body mass index is 27. She does not use tobacco but smokes marijuana once a week.

Which of the following best characterizes disengagement in persons living with MDD?

a. Disengagement is largely an emotional phenomenon
b. Disengagement is not associated with workplace-related function
c. Disengagement involves multiple domains of experience and manifests across multiple patient-reported outcomes
d. Disengagement is not related to general cognitive functions in MDD

PATIENT FACTORS AFFECTING LIFE ENGAGEMENT

Dr Correll asked if there are any caveats to including life engagement as a treatment goal. Dr McIntyre said that in his experience, engagement is "compartmentalized" for some patients. They would like to engage with a particular part of their life but may not be able to do so at the moment, owing perhaps to psychodynamic reasons or trauma; however, engagement in that area might be revisited later. For these people, a wholesale "engagement" objective might not be appropriate.

Baseline level of engagement could also impact achievement of engagement goals. Dr Thase noted, "If you've never been a joyous, libidinous, engaged person, your chances to become one at age 30 or 35 are diminished. It's harder to be better than your premorbid self, unless you've identified another functional characteristic of your premorbid self that might be treatable. Given that caveat though...very few people will tell us that they meet that restrictive category. Most people have experienced a better life before they became ill, and we should clarify what that better life entails."

LIFE ENGAGEMENT AND CURRENT TREATMENT OPTIONS

Life Engagement and Treatment Selection in MDD

Dr Thase said that he believes "the pathways to pleasure involve dopamine, and to a lesser extent norepinephrine" and so, from one perspective, the antidepressant with the most life-affirming therapeutic profile might be bupropion. The positive effect of dopaminergic agents on quality of life is quite likely driven by improvement of interest, pleasure, energy, and sexual and cognitive functioning and reduction of fatigue.[17] Dr Thase emphasized, though, that the first order of business is to get the person better and out of the current episode. If a particular medication has helped in the past, then that should drive the medication choice, and treatment can be fine-tuned later. Dr McIntyre picked up the focus on individual patients' needs:

> In thinking about psychosocial and pharmacotherapeutic treatments, the question that was interesting to us *yesterday* is, Which treatments are more effective? The question that's more interesting today and in the future is, Which treatments are more effective for which specific dimension or domain, and in which patients? We are seeing differences across modalities, as well as within modality, in their ability to affect aspects of functioning, of hedonism and cognition, and perhaps also engagement. Now that we have an established, validated framework for life engagement, the next question is, Do we have treatments that can engage aspects of life engagement that are known to be abnormal in depression?

Augmentation Strategies

Many patients have inadequate response to antidepressant monotherapy,[18] and augmentation strategies appear to be more beneficial than switching within or between classes of antidepressants.[19] Dr Thase said that among patients with inadequate response to antidepressants, lack of motivation is a common non-core symptom and that, for such patients, improving life engagement "has less to do with the first choice of treatment than perhaps the second or third choice of treatment." Symptoms of low life engagement, such as anhedonia, are frequent drivers of adjunctive antipsychotic prescription in MDD.[20]

Dr Thase noted that not all antidepressants or adjunctive strategies are equal at the individual-patient level. Further, he said, of the available augmentation therapies, dopamine partial agonists have the most life-affirming effects for people with difficult-to-treat depression. Of the 3 medications in this class, aripiprazole and brexpiprazole are FDA-approved for augmentation in MDD. Dr McIntyre noted that although the evidence is mixed regarding efficacy of cariprazine as augmentation in MDD,[21,22] its effects on hedonic tone and possibly cognition are of interest in terms of life engagement.

Brexpiprazole is the dopamine partial agonist that has been studied most with regard to life engagement. Data from clinical trial exit interviews suggested that patients were more engaged with life and calmer following treatment with adjunctive brexpiprazole compared to the pretreatment baseline, with 88.6% of patients describing improvements consistent with at least 1, and most commonly 2 or 3, of the 4 domains of life engagement (emotional, physical, social, and cognitive).[6] Analyses of clinical trials data based on the IDS-SR_{10} Life Engagement subscale also indicated a benefit for adjunctive brexpiprazole, with improvement on items reflecting "hot" cognition, motivation, energy, capacity for pleasure, and subjective well-being.[10]

Patient Perspectives

Improved engagement with life after brexpiprazole treatment in patients with MDD or schizophrenia was reflected in spontaneous calls made to the drug manufacturer's call center[10]:

"I felt like myself again"

"Like a light switch turned on and I had my old life back"

"It's like sunshine"

"I've been feeling pretty awesome; I've completed more projects in the last two weeks than I have in the last 5 years because I have been feeling better"

Level of patient functioning. For some antidepressants, patients with MDD who have better functioning at baseline have better outcomes, with low functioning predicting diminished antidepressant response.[23,24] However, Dr McIntyre said, that might not be true for other treatments, especially in people who have the ability to improve aspects of engagement during treatment. Data from 3 studies revealed that improvement in life engagement seen with adjunctive brexpiprazole was greatest among patients with MDD who have *lower* functioning at baseline.[25] Dr McIntyre noted that other atypical antipsychotics could be investigated in this regard as well.

Side effects. Augmentation of antidepressants with atypical antipsychotics is more effective versus placebo for remission (odds ratio = 2.00),[26] but it is also associated with discontinuation due to adverse events.[27] Patients should be made aware of potential side effects and be encouraged to report them. With regard to life engagement, Dr Thase commented, "It's hard to be engaged when you're sleepy, and it's hard to be amorous when you can't have an orgasm…the side effect profiles of some medications do affect what might be possible with that medication."

Of the agents approved by the FDA as adjunctive treatments for MDD, quetiapine extended release and olanzapine-fluoxetine combination are associated

with weight gain and sedating side effects (which, the experts noted, could interfere with life engagement), and aripiprazole is associated with activating side effects.[28] Aside from apathy and amotivation, symptoms of *overactivation* (agitation, hostility, irritability) are also key drivers for antipsychotic use in MDD,[20] so clinicians should keep activation-related side effects in mind when considering treatment options.

Psychosocial and Other Nonpharmacologic Interventions

Dr Rafeyan emphasized the importance of encouraging patients to follow appropriate diets and exercise as much as possible. That by itself, he noted, can have a tremendous impact on improvement of symptoms. Picking up this point, Dr McIntyre stated that building exercise into the treatment plan may enhance social function and combat the "pandemic" of loneliness seen in recent years. Normalizing sleep hygiene is important too; he pointed out that "it's hard to be engaged if you're exhausted."

The panelists endorsed combining psychotherapy with medication. As Dr McIntyre put it,

> The question, What's more effective: psychotherapy or antidepressants? is not interesting anymore. The question now is, Which therapy is more effective for which symptoms? Psychotherapy alone may not be as effective as medication for improving cognition or hedonistic to ne. But combining psychotherapy with medication may be the way to go—the idea being that 'one plus one equals three.'

He summarized the strategy: "We should aim for *rational* multimodality treatments that not only bring about remission on a rating scale but also achieve the engagement goals that patients prioritize."

Discussion of Case Practice Question

Preferred response is (c) Disengagement involves multiple domains of experience and manifests across multiple patient-reported outcomes.

Engagement involves aspects of cognitive, emotional, behavioral, and social functions. Disengagement is a highly distressing aspect of MDD, and persons living with depression often complain that it is a persisting phenomenon, despite antidepressant treatment. Some psychotropic agents and strategies may have differential effects on engagement. Engagement outcomes can be measured by measurement-based care.[7]

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