AJMC® CONFERENCE REPORT
THE AMERICAN JOURNAL OF MANAGED CARE®

US PSYCH CONGRESS 2017

Exclusive Coverage of the

2017 US PSYCHIATRIC AND MENTAL HEALTH CONGRESS

September 16-19 | New Orleans, Louisiana

Advances in Understanding Major Depressive Disorder: Looking Beyond Monoaminergic Pathways

A presentation discussing the emerging science in the diagnosis and management of major depressive disorder (MDD) was given by Andrew J. Cutler, MD, chief medical officer at Meridien Research Group and Florida Clinical Research Center, LLC, in Bradenton, Florida, on behalf of Alkermes plc at the 30th Annual US Psychiatric & Mental Health Congress, which was held September 16-19 in New Orleans. The presentation was designed to increase clinicians' awareness of the expanding role of multiple pathways in the management of MDD and to review how these pathways may be effectively targeted by future therapies.

According to the results of a recent survey completed by the World Health Organization, the estimated lifetime prevalence of MDD in adults in the United States is 16.6%, making

(Continued on page 2)

DSM-5 Specifier Aids Screening Anxiety With Depression

Major depressive disorder frequently appears with other disorders and comorbidities; experts say it is more the rule than the exception. However, before the *Diagnostic and Statistical Manual for Mental Health Disorders, Fifth Edition (DSM-5)* was published in 2013, the presence of anxiety in some patients may have been missed.

The addition of the anxious distress specifier in the *DSM-5* has simplified the task of identifying those patients whose anxiety must be considered in their treatment plan, said Mark Zimmerman, MD, director of outpatient psychiatry and of the Partial Hospital Program at Rhode Island Hospital, and a professor of psychiatry at The Warren Alpert Medical School of Brown University, both in Providence, Rhode Island.

During a presentation at the recent 30th Annual US Psychiatric and Mental Health Congress in New Orleans, Louisiana, Zimmerman said study results have indicated that the presence of comorbid disorders or specific symptoms were the most important

(Continued on page 4)

ALSO IN THIS ISSUE

Michael J. Hennessy Associates, Inc.

Understanding Major Depressive Disorder (Continued from page 1)

it one of the most common mental health disorders in the United States.[1,2] The incremental economic burden of MDD to the individual increased from $173.2 billion in 2005 to $210.5 billion in 2010, which represents an increase of 21.5%. This can largely be attributed to the rising costs incurred from comorbid conditions related to MDD.[3]

The presence of MDD increases the risk for the development of multiple diseases, including heart disease, hypertension, stroke, diabetes, Alzheimer's disease, obesity, and cancer. In addition, depression appears to be linked to an increased risk of overall mortality.[4] These comorbid conditions may develop for a variety of reasons. Depressed patients typically follow a less healthy lifestyle than nondepressed patients; they are more likely to smoke, drink alcohol excessively, follow an unhealthy diet, and exercise less.[4] In addition, data suggest that there may be a potential biological dysregulation of multiple pathways that occurs in depressed patients. These dysregulations may include metabolic, immuno-inflammatory, autonomic, and hypothalamic-pituitary-adrenal axis mediated changes, which may also contribute to the increases to the presence of comorbid conditions.[4]

Management of MDD can be difficult, as patient-specific symptoms are often highly variable. "Achieving response or remission can be challenging with a first-line agent in many patients," according to Cutler.

Response to therapy in MDD was evaluated in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial, was a series of randomized, controlled treatment trials in patients with MDD (n = 3671). Patients who did not achieve remission or could not tolerate their initial therapy were encouraged to proceed to the next treatment step (therapy switch or augmentation).[5] The trial found that only 36.8% of patients achieved remission from their first-line therapy. Rates of remission actually decreased with each additional switch in medication therapy; however, augmentation with an additional antidepressant medication provided a relatively improved rate of remission versus switching alone.[5] This study highlights the difficulties of treating patients with MDD and the lengthy stepwise approach that is often required.

Although remission is an important goal in patients with MDD, residual symptoms of MDD may still be present in this disease state. The presence of residual symptoms in patients with partial remission of MDD have demonstrated a strong correlation with the risk of subsequent early relapse of MDD.[6] Therefore, it is important to not only get patients with MDD to remission, but to also minimize the number of residual symptoms they exhibit in order to be most effective in preventing subsequent relapse.

Achieving full or partial remission in MDD can be challenging due to the complexity of symptoms and interpatient variability. Treatment adherence can be increased by developing a patient-centered care plan in partnership with the patient. An individualized treatment plan should consider the patient's severity of symptoms, presence of co-existing conditions, psychosocial stressors, patient preference, and treatment history.[7] In addition, an ongoing relationship must be established with the patient to determine the potential benefits and adverse effects of treatment on a regular basis. Systematic assessments using a clinician and/or patient-administered rating scale may be useful during initial and subsequent evaluations in order to track the patient's progress and make treatment adjustments as necessary.[7]

Just as the symptoms of MDD can be highly variable, emerging research indicates that the pathways and processes involved in the development of MDD may be more variable than once thought. Although all current FDA-approved antidepressant therapies primarily target and modulate monoamine pathways (serotonin, norepinephrine, and dopamine).[8] Current

research efforts are examining the hypothesis that depression may be linked to additional pathways and processes outside of the manipulation of monoamines.[9]

The neuroplasticity hypothesis of depression involves understanding the ability of the brain to develop and mature neurons (neurogenesis) or synapses (synaptogenesis) and to understand how and why patients with MDD may have a dysfunction in this process.[9] Brain scans of patients with MDD have demonstrated a reduction in grey matter compared with healthy controls.[10] Patients with MDD also have been found to have a reduced number of synapses in the prefrontal cortex compared with healthy controls.[11] Interestingly, recent research has shown that currently available antidepressants may also enhance neurogenesis and synaptogenesis.[9]

Glutamate signaling is another area of interest in MDD research. Glutamate is a neurotransmitter thought to have effects on synaptic plasticity, learning, and memory. Study results demonstrate changes in glutamate receptors among patients with MDD, as well as elevated levels of glutamate in the brain.[12] When glutamate signaling is impaired, such as in stress or depression, neuroplasticity of the brain may also be affected.[13]

Increased cholinergic activity and decreased noradrenergic activity are also thought to be associated with the development of depressive symptoms. Anticholinergic agents have shown some antidepressant effects, which may be mediated through a downstream increase in neuroplasticity of the brain.[9]

Neuroinflammation due to chronic stress may play an additional role in the development of depression. Stress can activate pro-inflammatory cytokines, which can exert direct neurotoxic effects on regions of the brain involved in the regulation of emotions. Over time, the activation of this pathway may clinically present as symptoms of depression.[14]

Understanding the role that the endogenous opioid system plays in MDD has been another recent area of interest. This system includes 3 key neurotransmitters: beta endorphin, enkephalin, and dynorphin, and the receptors associated with these neurotransmitters are the mu opioid receptor, the delta-opioid receptor, and kappa opioid receptor. The endogenous opioid system plays an important role in analgesia, addiction, and modulation of emotion and stress responses.[15] The results of a recent study in women demonstrate that during sustained states of sadness, patients with MDD have an altered opioid binding potential versus healthy patients, which suggests a pattern of altered endogenous opioid signaling in MDD.[16]

Each of the 3 receptor types has a unique effect on mood regulation:[17]

- ***Mu opioid receptors:*** Commonly identified for their role in analgesia and reward. Overstimulation of these receptors is often implicated in substance abuse and addiction. Mu opioid receptor agonism is associated with an improved mood and antidepressant-like effects for some, but not all individuals.
- ***Delta opioid receptors:*** These receptors appear to act similarly to mu opioid receptors. Receptor agonism is also linked to improved mood and antidepressant-like effects.
- ***Kappa opioid receptors:*** These receptors appear to act in contrast to the mu and delta receptors. Agonism of the kappa opioid receptor results in a depressant effect, while antagonism of the receptor is linked to antidepressant-like effects.[17]

> “MDD is not a singularly focused disease, but is a complex disorder involving multiple pathways and processes.”

Future research may help us understand the differences among the 3 receptor types and identify targeted therapy that can positively effect mood while balancing the unwanted effects of opioid receptor stimulation. As Cutler stated, “Achieving an antidepressant effect through modulation of the endogenous opioid system may involve appropriately balancing activity of the 3 key receptors.”

Increased understanding of the complexity and multiple potential pathways involved in MDD may be the key to identifying ways to help more patients achieve remission. It is becoming clear that MDD is not a singularly focused disease, but is a complex disorder involving multiple pathways and processes, which may or may not be activated in all patients. According to Cutler, “Further research is warranted to better understand the pathways beyond the monoamines in the cause and treatment of MDD.” ●

REFERENCES

1. Kessler RC, Sampson NA, Berglund P, et al. Anxious and non-anxious major depressive disorder in the World Health Organization World Mental Health Surveys. *Epidemiol Psychiatr Sci*. 2015;24(3):210-226. doi: 10.1017/S2045796015000189.

2. National Institute of Mental Health. Major depression among adults. NIMH website. nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml. Accessed September 26, 2017.

3. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015;76(2):155-162. doi: 10.4088/JCP.14m09298.

4. Penninx BW, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med*. 2013;11:129. doi: 10.1186/1741-7015-11-129.

5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163(11):1905-1917.

6. Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A. Residual symptoms after partial remission: an important outcome in depression. *Psychol Med*. 1995;25(6):1171-1180.

7. Work Group on Major Depressive Disorder. Practice guideline for the treatment of patients with major depressive disorder, third edition. American Psychiatric Association website. psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Published October 2010. Accessed September 27, 2017.

8. Alkermes plc. Major depressive disorder: looking beyond monoaminergic pathways. Slides presented at: US Psychiatric & Mental Health Congress; September 19, 2017; New Orleans, Louisiana. www.challengemdd.com/pathophysiology-of-mdd. Accessed October 10, 2017.

9. Dale E, Bang-Andersen B, Sánchez C. Emerging mechanisms and treatments for depression beyond SSRIs and SNRIs. *Biochem Pharmacol*. 2015;95(2):81-97. doi: 10.1016/j.bcp.2015.03.011.

10. Zhao YJ, Du MY, Huang XQ, et al. Brain grey matter abnormalities in medication-free patients with major depressive disorder: a meta-analysis. *Psychol Med*. 2014;44(14):2927-2937. doi: 10.1017/S0033291714000518.

11. Kang HJ, Voleti B, Hajszan T, et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nat Med*. 2012;18(9):1413-1417.

12. Duric V, Banasr M, Stockmeier CA, et al. Altered expression of synapse and glutamate related genes in post-mortem hippocampus of depressed subjects. *Int J Neuropsychopharmacol*. 2013;16(1):69-82. doi: 10.1017/S1461145712000016.

13. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med*. 2016;22(3):238-249. doi: 10.1038/nm.4050.

14. Kim YK, Won E. The influence of stress on neuroinflammation and alterations in brain structure and function in major depressive disorder. *Behav Brain Res*. 2017;329:6-11. doi: 10.1016/j.bbr.2017.04.020.

15. Benarroch EE. Endogenous opioid systems: current concepts and clinical correlations. *Neurology*. 2012;79(8):807-814. doi:10.1212/WNL.0b013e3182662098.

16. Kennedy SE, Koeppe RA, Young EA, Zubieta JK. Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. *Arch Gen Psychiatry*. 2006;63(11):1199-1208.

17. Lutz PE, Kieffer BL. Opioid receptors: distinct roles in mood disorders. *Trends Neurosci*. 2013;36(3):195-206. doi: 10.1016/j.tins.2012.11.002.

***DSM-5* Specifier** (Continued from page 1)

factors driving treatment decisions when clinicians selected an antidepressant for a patient, and anxiety was the symptom they cited most frequently (19.9%).[1]

For patients to meet the criteria of the anxious distress specifier, they must have 2 of the following 5 symptoms across an episode: 1) feeling keyed-up or tense; 2) feeling unusually restless; 3) having difficulty concentrating because of worry; 4) feeling fear that something awful might happen; and 5) feeling that one might lose control of oneself.[2]

Anxiety actually affects about 50% of patients with depression, Zimmerman said. That covers a lot of ground: He led a study of 773 depressed patients, with results indicating that 17.1% had panic disorder, 33% had social phobia, 13.4% had posttraumatic stress disorder (PTSD), and 15% had general anxiety disorder.[3]

Despite the numbers, social phobia was frequently overlooked, he said. This means that many patients with anxiety are missed. "It's just the reality of a busy clinical practice," Zimmerman said.

However, finding better ways to screen patients for anxiety is important, because, according to Zimmerman, study results show that more than 75% of patients with anxiety say they want to be treated.

Zimmerman described a 2-stage screening process to the audience. The first stage screens for general distress, and if the patient tests positive, a second, more in-depth stage determines a more precise diagnosis.

Next, Zimmerman reviewed clinical trial data involving patients with anxious depression. He explained that there have been relatively fewer studies involving patients with depression and anxiety because they have often been excluded from trials. These patients have greater psychosocial impairment, and poorer, slower response to treatment. A literature review involving 31 studies concluded that:

- Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants are effective in treating anxious depression.
- Patients with anxious depression have poorer outcomes and experience more/greater adverse effects.
- Patients with anxious depression often do not have sustained outcomes after initial success with a new drug.[4]

Guidelines regarding recommended antidepressants vary by country. British guidelines did not find much difference among antidepressants for treating anxiety, Zimmerman said, but the American Psychiatric Association made several specific recommendations for SSRIs (good for social anxiety disorder with depression, PTSD, and obsessive-compulsive disorder [OCD]), bupropion (comparable with SSRIs for low to moderate levels of anxiety), and clomipramine (effective for OCD with depression).[5]

Testing the Anxious Distress Specifier

Some studies of the anxious distress specifier have not actually measured all 5 criteria because databases did not have information on all 5 measures. Zimmerman's research group came up with ways to measure all 5. His group tested a scale for the new anxious distress specifier, called Clinically Useful Outcome Scale, or CUDOS; the study with 773 outpatients with depression found the scale to have high retest reliability, and good discriminant and convergent validity.[6] Because the specifier is supposed to measure symptoms across an episode, Zimmerman's group also came up with an interview measure; once again, the specifier held up to clinician and self-reported assessments of anxiety and depression.

Some of the group's work suggests that the new specifier may produce different results than would older anxiety-measurement scales. This discrepancy is an area for future research, Zimmerman said. "Hopefully the anxious distress specifier is as good if not better at [assessing] impairment, functioning, and predicting outcomes," because it's so much easier to administer, he noted. "Hopefully, it's a more clinically useful way of assessing anxiety."

Clinical guidelines, however, suggest that there is no best or worst antidepressant for highly anxious depressed patients, which can leave much to the individual prescribing practices of the psychiatrist.

The *DSM-5* anxious distress specifier does represent a step forward, Zimmerman said: "Screening can improve detection. It can improve the efficiency of the diagnostic process." ●

REFERENCES

1. Zimmerman M, Posternak M, Friedman M, et al. Which factors influence psychiatrists' selection of antidepressants? *Am J Psychiatry*. 2004;161(7):1285-1289. doi: 10.1176/appi.ajp.161.7.1285.

2. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Health Disorders, Fifth Edition.* Arlington, VA: American Psychiatric Association; 2013.

3. Zimmerman M, McDermut W, Mattia JI. Frequency of anxiety disorders in psychiatric outpatients with major depressive disorder. *Am J Psychiatry*. 2000;157(8):1337-1340. doi: 10.1176/appi.ajp.157.8.1337.

4. Ionescu DF, Niciu MJ, Richards EM, Zarate CA Jr. Pharmacological treatment of dimensional anxious depression: a review. *Prim Care Companion CNS Disord*. 2014;16(3). doi: 10.4088/PCC.13r01621.

5. Gelenberg AJ, Freeman MP, Markowitz JC, et al, eds. *Practice Guidelines for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Washington, DC: American Psychological Association; 2010.

6. Zimmerman M, Chelminski I, Young D, Dalyrymple K, Walsh E, Rosenstein L. A clinically useful self-report measure of the *DSM-5* anxious distress specifier for major depressive disorder. *J Clin Psychiatry*. 2014;75(6):601-607. doi: 10.4088/JCP.13m08961.

Patient Perspectives Contribute to the Management of Major Depressive Disorder Symptoms

Major depressive disorder (MDD) is a widespread health problem affecting a growing number of individuals in the United States. Between 2005 and 2010, MDD prevalence increased from 13.8 million to 15.4 million adults in the United States alone.[1] The World Health Organization also estimates that the number of people living with depression increased to 322 million (an increase of 18.4%) between 2005 and 2015.[2] Also, mental and behavioral disorders are the leading cause of years lived with disability (YLDs) in the United States, with MDD contributing the highest percentage of YLDs.[3,4] Individuals diagnosed with severe depression often experience a reduced quality of life and higher rates of cardiovascular disease, diabetes, and overall mortality.[5,6] However, because MDD is chronic and heterogeneous, no standard definition exists and no established method can explain all facets of the disease.[5,7] Many individuals receive inadequate treatment for depression, either because they are unwilling to seek help or because healthcare providers fail to detect a problem.[8]

At the 30th US Psychiatric and Mental Health Congress in New Orleans, Louisiana, September 16-19, 2017, investigators from Alkermes, Inc (Waltham, Massachusetts) and the Depression and Bipolar Support Alliance (DBSA; Chicago, Illinois) presented data focused on the patient perspective of dealing with the challenges of living with MDD.[9,10]

Gaining a better understanding of the patient experience is an important part of improving depression treatment. Results from previous studies have shown that patients appreciate personal support and benefit from a continuous relationship with a depression care specialist.[11,12] Another study reported that patients who received telephone support and detailed treatment recommendations after their first primary care visit, had lower mean depression scores at follow-up than those who did not receive such support.[13] These results suggest that a personalized approach to depression treatment is warranted.

Doederlein et al presented a study designed to better identify the experiences and challenges faced by individuals with depression and to determine patient-preferred treatment approaches.[9] Study participants were asked to respond to a 22-item survey designed to document depression symptoms, wellness strategies, and treatment plans. The survey was based on interview data collected from a panel of individuals with depression who did not adequately respond to treatment with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norephinephrine reuptake inhibitors (SNRIs). An online survey was conducted between February and April 2016 by DBSA.[9] The cross-sectional study used frequency and percentage statistics to summarize the findings. Participants were split into 3 groups based on treatment plan effectiveness; the 3 groups were defined as those who found their plan to be effective, those who did not, and those who thought it was partially effective. Using χ2-square tests, the researchers compared the different treatments and symptoms across the 3 groups.[9]

In an analysis of patient-reported responses collected from 387 individuals who completed all the questions in the survey, researchers found that the most commonly reported depression symptoms included irritability (93%), loss of energy (89%), and prolonged sadness (86%).[9] Patients who found an effective treatment plan were less likely to exhibit feelings of guilt, loss of energy, or an inability to find pleasure in activities, in comparison with patients who were unhappy with their current treatment plans.[9] Approximately 75% of respondents reported using medications to treat their depression and about 16% of patients used 10 or more medications.[9] Additional treatment modalities, including psychotherapy or wellness strategies, were used to manage depression in over half of the respondents. Playing with children or pets and listening to music were the most reported wellness strategies.[9] In managing their depression, 37.5% of patients used more than 2 treatment plans. In addition,

> “Gaining a better understanding of the patient experience is an important part of improving depression treatment.”

patients who used medications, psychotherapy, peer support groups, or wellness strategies were more likely to feel that their treatment plan was effective compared with those who did not use such treatments (all $P < .05$).[9] Furthermore, patients using more than 3 treatment modalities were more likely to report that their treatment plan was effective ($P < .001$).[9] In addition, patients who incorporated specific wellness strategies were more likely to report having found an effective treatment plan. These strategies included eating a balanced diet, exercising, meditating, doing breathing exercises, volunteering, getting enough sleep, spending time with friends, and taking part in a peer support group.[9] Individuals who incorporated 5 or more wellness strategies into their treatment plan were more likely to report that their treatment plan was effective than those who used fewer than 5 strategies ($P < .001$).[9]

Although survey data indicate that some combinations of treatments and wellness strategies were associated with finding an effective treatment plan, only 27% of respondents indicated that they had found an effective treatment plan to manage their depression.[9] The authors note that the survey data are limited to patients within the DBSA network who had completed the entire survey, and the cross-sectional nature of the survey does not allow for assessment of changes in depression symptoms over time.[9] According to the research, multiple factors, such as plan type, symptoms, wellness strategies, and number of medications, can impact a patient's ability to find an effective treatment plan. Finally, the authors concluded that more medication options and a better understanding of methods for providing education and support for depression are needed.[9]

A complementary presentation by Mehta et al described a study aimed at better understanding the impact of the symptoms of depression on patients' daily lives, as well as assessing whether a self-reported sense of well-being correlated with physician-reported improvement of symptoms.[10] Study participants included patients with MDD who previously participated in a long-term safety and tolerability study of ALKS 5461, an investigational drug for the treatment of MDD that was recently submitted for FDA approval.[10,14] Participants were asked to rank the symptoms described in the 10-item Montgomery-Asberg Depression Rating Scale (MADRS) survey, with 1 being the most important and 10 being the least important. The impact of depression symptoms on daily activities, social life, and family life was also ranked (where 0 = no impact and 10 = extreme impact). Also, overall well-being regarding cheerfulness, feeling active or calm, and interest in life activities was ranked (where 0 = not well and 10 = very well). Questions relating to quality of sleep were also included.[10] Investigators calculated means and standard deviations (SDs) to rank the importance of symptoms, functional impact of depression, and overall well-being. The study authors searched for links between patient MADRS scores collected at the last day of the study with daily functioning and overall patient well-being.[10]

The survey was completed by 123 study subjects, for which the mean MADRS score was 12.1 (SD = 9.5). MADRS importance ratings, daily activities, well-being, and social and family life were not affected by race or gender.[10] Patients ranked “sadness,” “inability to feel,” and “concentration difficulties” as the most important MADRS symptoms.[10] Different antidepressant treatments did not have an effect on the MADRS ranking order.[10] Depression appeared to have a similar impact on daily activities, social life, and family and home life, with mean scores of 4.0, 4.5, and 4.2, respectively.[10] Unsurprisingly, patients stating that depression had a low impact on daily activities, social life, and family life also reported a higher level of well-being.[10] Additionally, investigators found significant correlations between patients' MADRS scores and the impact of depression on the ability to function and overall well-being ($P < .001$).[10]

Like the Doederlein et al study, the data presented by Mehta et al are limited, and the results are provisional due to the ongoing nature of the study. The study was restricted to patients who completed a long-term safety and tolerability study of an investigational drug for at least 3 months at the start of this study. Again, the cross-sectional survey design does not allow changes in depression symptoms at different time points to be assessed, making it difficult to characterize how depression makes an impact on daily life over time.[10] Nonetheless, these results indicate that depression symptoms do affect overall well-being and daily function and offer insights about the perceived levels of those effects (high, medium, or low).[10]

By analyzing depression from a patient perspective, researchers from the aforementioned studies were able to gain preliminary data that may help to shape the design and focus of future clinical trials and improve the types of support and wellness tools offered to patients with MDD.[9,10] Researchers are continually striving to improve treatment for the many patients who do not respond well to standard therapies. For example, investigators are integrating animal models and neurobiological approaches to human depression studies to learn more about human responses to depression treatment.[15] Advances in magnetic resonance imaging are allowing researchers to better study the effects of new antidepressants on neural circuits, and genomic studies are helping us to understand the role of genetics in depression. Emerging data suggest certain genes are associated with depression. These findings may inform new therapeutic approaches and aid in the development of more effective medications.[15] The patient perspective on of

depression, together with biology and genetic data, offers hope for improved depression treatments in the future. ●

REFERENCES

1. Greenberg PE, Fournier A-A, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry.* 2015;76(2):155-162. doi: 10.4088/JCP.14m09298.

2. Depression and other common mental disorders: global health estimates. World Health Organization website. apps.who.int/iris/bitstream/10665/254610/1/WHO-MSD-MER-2017.2-eng.pdf. Published 2017. Accessed September 27, 2017.

3. Leading category of diseases/disorders. National Institute of Mental Health website. nimh.nih.gov/health/statistics/disability/leading-category-of-diseases-disorders.shtml. Accessed September 28, 2017.

4. U.S. YLDs contributed by mental and behavioral disorders. National Institute of Mental Health website. nimh.nih.gov/health/statistics/disability/us-ylds-contributed-by-mental-and-behavioral-disorders.shtml. Accessed September 28, 2017.

5. Nemeroff CB. The burden of severe depression: a review of diagnostic challenges and treatment alternatives. *J Psychiatr Res.* 2007;41(3-4):189-206. doi:10.1016/j.jpsychires.2006.05.008.

6. Anderson RJ, Freedland KE, Clouse RE, Lustman, PJ. The prevalence of comorbid depression in adults with diabetes. *Diabetes Care.* 2001;24(6):1069-1078.

7. Otte C, Gold SM, Penninx BW, et al. Major depressive disorder. *Nat Rev Dis Primers.* 2016;2:16065. doi: 10.1038/nrdp.2016.65.

8. Collins KA, Westra HA, Dozois DJA, Burns DD. Gaps in accessing treatment for anxiety and depression: Challenges for the delivery of care. *Clin Psychol Rev.* 2004;24:583-616. doi:10.1016/j.cpr.2004.06.001.

9. Doederlein A, Deetz I, DePeralta D, et al. Patient's experience of challenges with symptoms and treatments for depression. Poster presented at: 30th U.S. Psychiatric and Mental Health Congress; September 16-19, 2017; New Orleans, Louisiana.

10. Mehta A, Sun X, Memisoglu A, et al. Depressive symptoms and their impact on functioning and overall well-being from a patient's perspective. Poster presented at: 30th U.S. Psychiatric and Mental Health Congress; September 16-19, 2017; New Orleans, Louisiana.

11. Dowrick C, Kokanovic R, Hegarty K, Griffiths F, Gunn J. Resilience and depression: perspectives from primary care. *Health.* 2008;12(4):439-452. doi: 10.1177/1363459308094419.

12. Hunkeler EM, Katon W, Tang L, et al. Long term outcomes from the IMPACT randomised trial for depressed elderly patients in primary care. *BMJ.* 2006;332(7536):259-263. doi: 10.1136/bmj.38683.710255.BE.

13. Simon GE, VonKorff M, Rutter C, Wagner E. Randomised trial of monitoring, feedback, and management of care by telephone to improve treatment of depression in primary care. *BMJ.* 2000;320(7234):550-554.

14. Alkermes initiates ALKS 5461 NDA for major depressive disorder. CenterWatch website. centerwatch.com/news-online/2017/08/22/alkermes-initiates-alks-5461-nda-major-depressive-disorder/. Published August 22, 2017. Accessed September 26, 2017.

15. Akil H, Gordon J, Hen R, et al. Treatment resistant depression: A multi-scale, systems biology approach [published online August 30, 2017]. *Neurosci Biobehav Rev.* doi: 10.1016/j.neubiorev.2017.08.019.

Papakostas Gives Update on Adding Therapy in Treatment-Resistant Depression

If a patient with major depressive disorder (MDD) fails to respond to therapy, what comes next? The answer is more complex than it once was, because the list of treatment options is growing, according to George I. Papakostas, MD, the scientific director for Massachusetts General Hospital Clinical Trials Network and Institute and an associate professor of psychiatry at Harvard Medical School, both in Boston, Massachusetts.[1]

Papakostas, who has won many awards for his work on the placebo effect, offered an update on treatment-resistant MDD (TRD), on September 18, 2017, at the US Psychiatric and Mental Health Congress in New Orleans, Louisiana.

"Often, after treating a patient with [an] antidepressant, we're going to have to follow up with a number of strategies in order to get them to full remission," he said, sharing results of a study he led that showed the response rate was 53.8% for antidepressants, compared with 37.3% for placebo.[2] "If you look at the placebo effect, it's not negligible. This isn't the field of oncology. This is the field of psychiatry."

The placebo effect can be frustrating, but also reinforces a powerful lesson that good care comes from a combination of the right therapy and the right people. "The exciting part is, in the clinic, this is a huge advantage," he said. "Beyond whatever treatments we use and our knowledge of these treatments, our ability to inspire patients to get better, to instill confidence in them, to feel cared for, is a huge therapeutic ingredient."

Still, it is essential to know that when a patient cannot achieve remission, Papakostas said, a key decision today is whether to switch therapy or to continue a current therapy while adding an adjunctive therapy—either by augmenting the antidepressant, or by using 2 in combination. Both routes have benefits and drawbacks, but "there's more and more evidence for augmentation," he said. "The question becomes, 'Can we do the same job while minimizing these multidrug risks?"

Papakostas said that when he sees a patient with TRD, he initiates a 5-part test:

- Has the patient received the right amount of treatment for the right duration of time? Was therapy structured, or was the patient "just sort of attending"?
- Is the diagnosis appropriate?
- Are there comorbidities that have gone unaddressed?
- Are there medication adherence or tolerability issues that have interfered with the success of the regimen?
- Are there pharmacokinetic factors in play, such as the patient being a rapid metabolizer of the drug?

When it comes to adherence, Papakostas is careful not to judge: The vast majority of patients who do not take medication simply forget, he said, adding, "I don't think I've ever been able to complete an antibiotic regimen with 100% compliance."

Switching Versus Adjunctive Therapy

Deciding to switch an initial course of treatment to a different therapy if the patient does not achieve remission should not

> A key decision today is whether to switch therapy or to continue a current therapy while adding an adjunctive therapy.

be without some considerations. The advantages of switching include limiting the risk of drug interactions, eliminating adverse effects if a therapy is not working, and limiting cost if the patient is already taking other drugs for medical issues. Adding too many drugs can complicate adherence, Papakostas noted. However, if a therapy had some benefits—just not a sufficient number—it may not be wise to risk withdrawal.

Here, he said, the physician faces a dilemma: "Should I complicate the regimen, or simplify the regimen?" Over the past 15 years, there has been more evidence for augmentation. Papakostas presented a host of studies supporting different therapy options, including some experimental ones.

Switching

A meta-analysis led by Papakostas compared patients with MDD who switched within the class of selective serotonin reuptake inhibitors (SSRIs) with those who switched from SSRIs to a drug outside the class. A total of 23.5% achieved remission switching within the SSRI class, compared with 28% who achieved remission by switching outside the class.[3] "That's not negligible, but the second SSRI can't be ruled out as a reasonable option," he said.

What if a patient fails 2 SSRIs? "No one has done that study, but I think at that point we can infer it's best to switch outside the class," Papakostas said.

Augmentation

Atypical antipsychotics have been studied the most, offering more than twice the remission benefit as placebo (47.4% vs 22.3%) for TRD across a meta-analysis that Papakostas and his co-authors published in 2007.[4] "That was impressive at the time, because most of these patients had failed 2 or more treatments," he said.

The downside here is that tolerability varies greatly by agent, including some agents that have significant neuroendocrine and metabolic effects. "The early signal confirmed our suspicions that this seemed to work but not every patient would be able to tolerate it," he said.

Lithium is also well studied as an augmentation agent, but there are few studies with newer agents, and the positive studies are all of short duration. Lithium also requires blood monitoring.

Papakostas has some experience with the mirtazapine-mianserin combination, which may help with insomnia as it has a sedative effect, but it can cause weight gain. Omega-3 fatty acids have been the subject of several studies; they are well tolerated and appear to offer cardiovascular benefits as well, he said.

In the Pipeline

Ketamine

"Soon the ketamine drugs will probably overtake the atypicals," Papakostas said during his talk, acknowledging the excitement over this potential fast-acting treatment. Intravenous ketamine, however, has its limitations, he said.

While several interventions have been studied, Papakostas noted that the one closest to approval involves an intranasal esketamine augmentation in TRD. He shared pooled results of phase 1 and 2 studies that were first presented at the American Society of Clinical Pharmacology meeting in 2015, which showed improvements in Montgomery-Asberg Depression Rating Scale scores as doses increased. "The higher the dose, the greater the response," he said.

ALKS 5461

Papakostas explained the mechanism of action of this combination of samidorphan and buprenorphine from Alkermes, which he said made complete sense to him when he first heard about it.

The result of combining samidorphan, a mu opioid antagonist, and buprenorphine, a mu agonist and kappa agonist, is a kappa opioid receptor antagonist. Why would this work as an augmentation, Papakostas asked?

When people take an opioid, he said, it blocks pain, and there may be a little bit of a high, but a number of people complain of a dysphoric reaction. Anyone who has taken an opioid after surgery and felt groggy and irritable will recall the effect, he said. But, Papakostas posed, "what if you block the endogenous opioid receptor agonist from getting to the kappa receptor by blocking the kappa receptor?"

With positive results from phase 2 and phase 3 studies now available, he said, "This is now sitting on FDA's table."

With so many choices, how do physicians decide what to use? Decisions between doctors and patients are complex, Papakostas said. "Safety is obviously paramount," along with tolerability, he noted.

Patient history and choice play large roles, too. "All things being equal," Papakostas concluded, "I always prefer to go with a patient's strong choice when we get to a decision point." ●

REFERENCES

1. Papakostas GI. Update on treatment-resistant major depressive disorder. Presentation at: Psych Congress; September 16-19, 2017; New Orleans, LA.

2. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized trials in MDD. *Eur Neuropsychopharmacol*. 2009;19(1):34-40. doi: 10.1016/j.euroneuro.2008.08.009.

3. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry*. 2008;63(7):699-704. doi: 10.1016/j.biopsych.2007.08.010.

4. Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry*. 2007;68(6):826-831.

Panel Explores Benefits of 16-Hour Window in Mydayis for ADHD

Physicians and nurse practitioners gathered at the 30th Annual US Psychiatric and Mental Health Congress in New Orleans in September from the 16th to the 19th for a panel discussion about the newly FDA-approved medication Mydayis. The discussion was led by Jennifer Ashton, MD, ABC News chief women's health news correspondent.

The need for patients 13 years and older with attention-deficit/hyperactivity disorder (ADHD) to take a midafternoon boost of medication could end with the arrival of Mydayis, a once-daily, mixed salts single-entity amphetamine that lasts up to 16 hours. It launched in August following its FDA approval on June 20, 2017.[1]

Ashton shared the data on ADHD, adding that the condition affects 1 in every 23 individuals, or 10.5 million adults, one of whom is her 19-year-old son. ADHD also affects more men than women. Increased awareness of ADHD, however, has not always translated into more treatment options.

Mydayis, which has the same active ingredient as Adderall XR, took more than 10 years and 16 studies before the FDA gave its approval. Clinical studies eventually involved more than 1600 patients and were summarized at the presentation.[1] Mydayis improved symptoms of ADHD as measured on the ADHD Rating Scale-IV and the Permanent Product Measure of Performance, a skills-adjusted math test.[2,3]

As the presentation demonstrated, the routine for many individuals with ADHD can be complicated: first comes the extended release (XR) amphetamine with breakfast, which starts working after about 30 minutes, peaks after about 4 hours, and tapers off all afternoon. Then comes the spike of the midafternoon dose of immediate-release (IR) amphetamine, which carries the patient through to the evening. Both audience members and the panel experts felt that care for adult patients with ADHD centers on getting them through the work day, not social settings. Panelist Rakesh Jain, MD, MPH, assistant professor of psychiatry at the University of Texas, explained, "the real experts," the patients, do not find this acceptable, and 81% report they have erratic days. "Some days are much worse than others; 44% of the patients said the afternoon was the most challenging time of the day."

Panelist Charles P. Vega, MD, a clinical professor of family medicine at the University of California, Irvine said that is not so unusual. "Symptoms at work tend to dominate the conversation among adult patients with ADHD; this is a holdover phenomenon from when they might have been experiencing symptoms at school. As a clinician, you want to address the most pressing needs of the patient, and so that means addressing the symptoms during the work day is important. But patients may lack the insight as to how their ADHD affects the other parts of their day." Both Vega and fellow panelist Alice Mao, MD, a board-certified psychiatrist at Baylor University in Waco, Texas, agreed that it is important to constantly assess and reassess how patients' responses are affecting their day, perhaps by speaking with a partner or family member.

> "Physicians in the room...overwhelmingly supported the idea of a single dose of amphetamine a day."

Patients with ADHD can use both pharmacologic and non-pharmacologic strategies, like coaching, Vega said. But what is clear from review of real-world data, he said, is that among patients using long-acting stimulants, 20% used more than 1 medication per day.

These needs demand a response, Jain said. "We cannot make ADHD their problem. It's our problem."

For the right patients, Mydayis offers the opportunity to get rid of that afternoon dip and spike—not to mention the problems that arise if patients forget to bring the IR medication to their afternoon class or job. A poll of audience members found 92% liked the idea of being able to give their patients a single pill in the morning compared with multiple pills throughout the day. Even if a different stimulant worked for a patient in the past, something new may be needed; for example, if the person has new responsibilities.

"ADHD is a condition that is dynamic," Jain said. "Needs change. Responses change."

The 3-Bead Technology

Kelly C. Lee, PharmD, MAS, BCPP, professor of clinical pharmacy at the University of California, San Diego explained the distinguishing feature of Mydayis: the 3-bead technology, which allows the active ingredient to be released at different times over the 16-hour period at different pH levels.[3] The first bead releases in the stomach, and the second and third beads release at different locations in the small intestine. The beads have different coatings to ensure their release points. A graphic of the pharmacokinetics of Mydayis in the presentation showed a continuous curve lasting up to 16 hours, with no interruptions or midafternoon spikes.[3]

It is important, said panelist Catherine Poulos, MPHNP-BC, a psychiatric nurse practitioner, that patients taking Mydayis develop a routine. It can be taken with or without food, but should be taken the same way each day. She tells patients to set a glass of water by the bedside as a reminder. If a dose is missed, it should not be taken late in the day. Instead, it should be the

next morning at the usual time. Lee said it is not appropriate for patients with a history of seizures and must be stopped if one occurs.[3]

Mydayis patients start at doses of 12.5 mg, with other doses available at 25, 37.5, and 50 mg. Results, however, have also been seen at lower doses (the higher doses are recommended only for adults, not individuals between the ages of 13 and 17).[3]

Poulos emphasized the need for constantly gauging patient needs. "I'm all about the reassessment—getting the right dose to the right patient." Jain, meanwhile, closed with the observation that the physicians in the room had overwhelmingly supported the idea of a single dose of amphetamine a day. "To me, that is the key."

Mydayis is approved for adolescents and adults age 13 and older only. Because it is an amphetamine, it has a black box warning for a high chance of abuse and dependence. Adverse effects include insomnia, decreased appetite, dry mouth, increased heart rate, anxiety, irritability, nausea, and weight loss.[3] ●

REFERENCES

1. U.S. FDA approves Mydayis (mixed salts of a single-entity amphetamine product) – a new once-daily option for ADHD symptom control in patients 13 years and older [news release]. Lexington, MA: Shire plc: June 20, 2017. shire.com/newsroom/2017/june/w6x937. Accessed October 5, 2017.

2. Adderral XR [package insert]. Lexington, MA: Shire US Inc; 2017.

3. Mydais [package insert]. Lexington, MA: Shire US Inc; 2017.

Seeking Sensible Cannabis Policy Requires "Balance," Says Beth Israel's Hill

The debate over marijuana policy tends to be dominated by people with political "skin in the game," when what is needed is a balanced, evidence-based review, said Kevin P. Hill, MD, MHS, of Beth Israel Deaconess Medical Center and Harvard Medical School, both in Boston, Massachusetts.

> "When talking about cannabis, whether it is with a patient or in the policy arena, it is essential to be balanced."

Marijuana is now legal in some form in 29 states and the District of Colombia, of which, 8 states and the District of Columbia allow recreational use.[1,2] But according to psychiatrist and addiction expert Hill, "It is not your father's weed out there." What's more, policy makers who fail to take an evidence-based approach when crafting laws for medical marijuana or decriminalization can leave loopholes or cause problems for their health systems.

Whether or not they agree with making cannabis legal, Hill said, it is important that health professionals follow what is happening so they that they can lend their expertise to lawmakers to help create policies that make sense. Hill, who recently became Beth Israel Deaconess' director of addiction psychiatry, is an assistant professor of psychiatry at Harvard Medical School and spoke at the 30th US Psychiatric and Mental Health Congress in New Orleans, Louisiana, in September.

"You've heard so much about cannabis in recent years, but, unfortunately, much of what you've heard is distorted or flat-out untrue," said Hill. The evidence about cannabis dispels the myths that marijuana is not harmful, that it is not addictive, and that people who use it do not suffer withdrawal, he added.

At the same time, not everyone becomes addicted, just as not everyone becomes addicted to alcohol, although about 15% of adults do. The share is less for cannabis at 9% of adults; that figure rises to 17% for those who start using cannabis while teenagers.[3] Although medical marijuana is often used to treat anxiety, there is insufficient support for this indication.[4,5] In addition, regular marijuana use may increase the chances of psychosis, especially if the patient has a family history of such conditions.[6]

Today's cannabis is far more potent than what was available a generation ago, Hill said; the average content of tetrahydrocannabinol, pot's psychotropic ingredient, is 12% compared with 3% to 4% in the 1960s through the 1980s. But the perception about cannabis is moving in the opposite direction—as rapidly as adults are taking up the drug, the idea that it poses no risk is climbing even faster, something that worries Hill, because it is just not true.

According to a 2015 National Survey on Drug Use and Health, almost 20 million individuals use cannabis each month, a number that has doubled in the past decade.[7-9] Marijuana's connection to other drugs is evident: In substance abuse programs, Hill said, 40% of patients are being treated for alcohol, 40% for opioids, and 20% for something else.

"When you sit down with these folks and you take a careful history," he said, "I found that about 60% of these patients would talk about a time in their lives when they were using cannabis daily for years, usually in their late teens or early 20s."

He and other researchers are focused on several areas:

- Identifying antiaddiction treatments that work
- Educating other clinicians about them
- Developing medications to aid withdrawal

When talking about cannabis, whether it is with a patient or in the policy arena, it is essential to be balanced, Hill said. Too often the debate is dominated by voices who have "political skin in the game." Marijuana is not completely harmless, but people who use it are not "doomed" either, he said. A young person who uses the drug "feels it's helping them in some way," and it is important for health professionals to acknowledge that.

Part of the challenge is that cannabis is viewed in extremes—to some it is all bad, and to others it is not harmful at all. Hill tries to compare cannabis with alcohol, which people know can be dangerous.

"There are different degrees of danger," Hill said. "Cannabis, on the whole, is probably not as dangerous as alcohol or opioids. But just because cannabis may not be as dangerous as alcohol or opioids, doesn't mean it's not dangerous."

It is important, for example, to understand the real effects of legalization. In Colorado, the first state to allow recreational use, marijuana use has been relatively unchanged, a statistic consistent with national trends.[10] However, Hill said there has been a rise in synthetic marijuana use among professional athletes, because users are trying to avoid getting caught during drug testing—so they use a more dangerous product.

Crafting Better Marijuana Policy

Using Massachusetts as an example, Hill pointed out areas where policies fell short on science:

- ***Quantities.*** While Massachusetts waits for marijuana to be available for recreational use legally, it does allow for use of medical marijuana, as long as it does not exceed the equivalent of 10 ounces for a 60-day supply. But Hill's studies show that amount is 4 times what most people would need.[11]
- ***Indications.*** Massachusetts' law allowed doctors to add additional medical reasons for marijuana certificates beyond those spelled out in the law. A review found 90% of the certificates were for undisclosed reasons.[12]
- ***Financial incentives.*** Hardship granted to low-income patients allowing them to grow their own supply are an invitation for problems.
- ***Fraud.*** A low-income patient on MassHealth, Massachusetts' Medicaid and State Children's Health Insurance Program, can get permission to grow marijuana to treat migraines, but does not need the entire supply and can make an under-the-table income selling the rest. Hill calculated the street value of a typical excess crop at $19,200 a year. ●

REFERENCES

1. States forge path through uncharted territory to legal pot. *USA Today* website. usatoday.com/story/news/nation-now/2017/07/31/marijuana-across-the-usa/511477001/. Published July 31, 2017. Accessed September 27, 2017.

2. State medical marijuana laws. National Conference of State Legislatures website. ncsl.org/research/health/state-medical-marijuana-laws.aspx. Published September 14, 2017. Accessed September 26, 2017.

3. Is marijuana addictive? National Institute on Drug Abuse website. drugabuse.gov/publications/research-reports/marijuana/marijuana-addictive. Updated August 2017. Accessed September 26, 2017.

4. D'Souza DC, Perry E, MacDougall L, et al. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. *Neuropsychopharmacology*. 2004;29(8):1558-1572. doi: 10.1038/sj.npp.1300496.

5. Turna J, Patterson B, Van Ameringen M. Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? [published online June 21, 2017]. *Depress Anxiety*. doi: 10.1002/da.22664.

6. Vadhan NP, Corcoran CM, Bedi G, Kelip JG, Haney M. Acute effects of smoked marijuana in marijuana smokers at clinical high-risk for psychosis: a preliminary study. *Psychiatry Res*. 2017;257:372-374. doi: 10.1016/j.psychres.2017.07.070.

7. What is the scope of marijuana use in the United States? National Institute on Drug Abuse website. www.drugabuse.gov/publications/research-reports/marijuana/what-scope-marijuana-use-in-united-states. Updated August 2017. Accessed September 27, 2017.

8. Prevalence of marijuana use among US adults doubles over past decade [news release]. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism; October 21, 2015. niaaa.nih.gov/news-events/news-releases/prevalence-marijuana-use-among-us-adults-doubles-over-past-decade. Accessed September 26, 2017.

9. Nationwide trends. National Institute on Drug Abuse website. drugabuse.gov/publications/drugfacts/nationwide-trends. Updated June 2015. Accessed September 27, 2017.

10. Wang GS, Hall K, Vigil D, Banerji S, Monte A, VanDyke M. Marijuana and acute health care contacts in Colorado [Published online March 30, 2017]. *Prev Med*. doi: 10.1016/j.ypmed.2017.03.022.

11. Guidance for law enforcement regarding the medical use of marijuana. Massachusetts.gov website. Medical Use of Marijuana, Department of Public Health, The Commonwealth of Massachusetts website. mass.gov/eohhs/docs/dph/quality/medical-marijuana/law-enforcement-guidance.pdf. Published April 15, 2015. Accessed September 27, 2017.

12. Feathers T. Most medical-pot permits issued for undisclosed conditions. *Lowell Sun* website. lowellsun.com/todaysheadlines/ci_28889191/most-medical-pot-permits-going-unqualified-patients. Updated September 28, 2015. Accessed September 27, 2017.