Final Consensus Panel Recommendation Statements and Mean Ratings[a]

Topic 1: Overcoming Barriers to Initiation and Use of Auvelity in the Treatment of Major Depressive Disorder	**Mean agreement**
Barrier #1: The unique mechanism of action (MOA) of Auvelity may create uncertainty in health care providers (HCPs) considering use of Auvelity for the treatment of MDD	
• **Statement 1a:** The medical field should provide education to healthcare providers (HCPs; eg, psychiatrists, PCPs, NPs, PAs, pharmacists, etc.) regarding the proposed MOA of Auvelity and how it differs from traditionally-used antidepressant medications.	**4.0**
• **Statement 1b:** HCPs should be informed that primary safety concerns are noted in the Auvelity label, including drug interactions with potent CYP2D6 inhibitors, concomitant use of dextromethorphan and/or bupropion-containing substances, cumulative risk of serotonin syndrome, and dangers of comorbid substance use disorder. HCPs should understand that although the MOA is unique, the safety warnings and precautions are similar to other antidepressants for MDD.	**3.9**
Barrier #2: HCPs need guidance about the type of patient most appropriate for use of Auvelity	
• **Statement 2a:** Auvelity is indicated for monotherapy in MDD and is recommended as an initial first-line treatment option offering the potential for a rapid response. Auvelity should be considered for those with a preference to avoid common side effects reported with other antidepressants (e.g., cognitive impairment, sexual dysfunction, weight gain, sleep disturbance, lack of energy, emotional blunting, etc.), and for those with MDD experiencing significant functional impairment.	**3.8**
• **Statement 2b:** Auvelity is recommended for those with an inadequate response, residual symptoms, and/or intolerable side effects associated with prior treatment.	**4.0**
• **Statement 2c:** Auvelity is not approved for individuals with treatment-resistant depression (TRD), psychotic disorders, or bipolar disorders. Auvelity can be used with caution for persons taking multiple medications and those with poorly controlled medical conditions.	**3.6**
• **Statement 2d:** Use of Auvelity in MDD is an appropriate treatment for individuals who also have symptoms of anxiety.	**3.8**
Barrier #3: Some HCPs need guidance about how to initiate Auvelity, or switch from current antidepressant therapy to Auvelity.	
• **Statement 3a:** When initiating Auvelity, monitor for efficacy or adverse events. Refer to Auvelity Prescribing Information for specific guidance.	**4.0**
• **Statement 3b:** Be mindful of drug interactions and associated risks with Auvelity. Refer to the section below entitled “Approaches for Initiating or Switching to Auvelity for Treatment of Major Depressive Disorder” for guidance on switching to Auvelity or adding Auvelity to an existing regimen.	**4.0**
• **Statement 3c:** In case of neuropsychiatric reactions during treatment with Auvelity, assess for other potential causes (eg, psychiatric disorders, medications, substance-related, other medical conditions) and address appropriately. If none are determined, discontinue Auvelity and monitor.	**3.8**

• **Statement 3d:** Based on animal studies, Auvelity could cause embryo-fetal harm and should be discontinued in pregnant females and those actively trying to become pregnant. Patients and HCPs should be encouraged to report exposures to Auvelity during pregnancy to the National Pregnancy Registry for Antidepressants.	**3.8**

Barrier #4: HCPs or patients may attempt do-it-yourself (DIY) use of over-the-counter (OTC) dextromethorphan as a combination therapy with bupropion rather than considering Auvelity	**Mean agreement**
• **Statement 4a:** Due to potential risks and a lack of evidence, HCPs should not combine bupropion with dextromethorphan-containing substances in lieu of prescribing Auvelity. HCPs should advise patients not to combine bupropion with dextromethorphan-containing substances instead of using Auvelity.	**4.0**
<u>Topic 2</u>: Approaches for Initiating or Switching to Auvelity for Treatment of Major Depressive Disorder	
A. Initiating Auvelity	
• **Statement 5a:** Initiate Auvelity once daily followed by increase to twice daily after 3 days.	**3.7**
B. Switching from current antidepressant therapy to Auvelity	
• **Statement 6a:** Consider utilizing measurement-based care (MBC) to monitor response and optimize outcomes when using antidepressant therapies.	**3.9**
• **Statement 6b:** Monitor for worsening depressive symptoms, suicidality, serotonin discontinuation syndrome, and serotonin syndrome.	**3.7**
• **Statement 6c:** Consider CYP2D6 inhibition when switching from SSRIs/SNRIs prescribed for MDD i. For SSRIs/SNRIs with low CYP2D6 inhibition (e.g., escitalopram, citalopram, sertraline, venlafaxine, desvenlafaxine): Consider prolonged up-titration of Auvelity with cross-taper of the SSRI/SNRI ii. For SNRIs with moderate CYP2D6 inhibition (e.g., duloxetine): Consider reducing SNRI to mid-range dose then cross-taper with Auvelity iii. For SSRIs with strong CYP2D6 inhibition (i.e., fluoxetine, paroxetine): Consider discontinuation and washout prior to initiating Auvelity	**3.7**
• **Statement 6d:** When switching from tricyclic antidepressants prescribed for MDD (e.g., amitriptyline, nortriptyline, imipramine): Consider appropriate discontinuation strategies and washout prior to initiating Auvelity.	**3.6**
• **Statement 6e:** When switching from MAOIs prescribed for MDD: MAOIs should be discontinued followed by a 14-day washout prior to initiating Auvelity	**4.0**
• **Statement 6f:** When switching from ketamine or esketamine prescribed for MDD: There are no systematic data available on how to switch to Auvelity from ketamine or esketamine. It may be possible to start Auvelity as early as the next day after discontinuing ketamine or esketamine although some panelists felt more comfortable initiating Auvelity 3-4 days after ketamine/esketamine dosing while the antidepressant effect persisted.	**3.3**
• **Statement 6g:** When switching the combination of an adjunctive atypical antipsychotic and an antidepressant prescribed for MDD, follow recommendations for switching another antidepressant to Auvelity and at the same time consider	**3.5**

adjusting the dose or discontinuing the atypical antipsychotic in either order as clinically appropriate.	

• **Statement 6h:** When switching from a multi-medication regimen prescribed for MDD: Prior to initiating Auvelity, appropriately discontinue any ineffective or poorly tolerated medications per medication guidance. Reduce or discontinue agents with potential for strong CYP2D6 inhibition.	**3.3**

C. Adding Auvelity to another antidepressant	**Mean agreement**
Recommendations with strong agreement (Rating: 3.5-4.0)	
• **Statement 7a:** Auvelity is indicated as monotherapy; currently, there are limited systematic data for use of Auvelity as adjunctive treatment.	**3.8**
• **Statement 7b:** Adding to atypical antidepressants prescribed for MDD: It may be appropriate to add Auvelity at standard doses to atypical antidepressants without significant CYP2D6 inhibition (e.g., vortioxetine, vilazodone, mirtazapine), but not to bupropion.	**3.9**
• **Statement 7c:** It may be appropriate to add Auvelity at standard doses to SSRIs/SNRIs without significant CYP2D6 inhibition (e.g., citalopram, desvenlafaxine, escitalopram, sertraline, venlafaxine) **i.** For SNRIs that moderately inhibit CYP2D6 (ie, duloxetine): Decrease to low or midrange dose or give only 1 tablet of Auvelity per day **ii.** Taper fluoxetine or paroxetine to low doses or discontinue prior to initiating Auvelity. Add Auvelity with caution to fluoxetine or paroxetine **iii.** Monitor for serotonin syndrome	**3.9**
• **Statement 7d:** Adding Auvelity to tricyclic antidepressants is not recommended due to potential safety concerns, especially in patients taking higher doses of tricyclics and patients over age 45 or with preexisting cardiovascular disease.	**4.0**
• **Statement 7e:** Adding Auvelity to MAOIs is contraindicated.	**4.0**
• **Statement 7f:** Adding Auvelity to NMDA antagonists used for MDD (i.e., ketamine, esketamine) may be done with caution.	**3.5**
• **Statement 7g:** Auvelity can be added to atypical antipsychotics. However, due to the CYP2D6 inhibition of bupropion, dosage adjustments of some atypical antipsychotics (eg, aripiprazole, brexpiprazole, cariprazine, risperidone) may be required.	**3.9**

[a] Mean score ≥3.0 on a 5-point Likert scale ranging from 0 (=do not agree) up to 4 (=very much agree). A criterion score of 3.0 represents approximately 75% agreement among the ten Delphi expert panelists; 3.0-3.4: moderate agreement; 3.5-4.0: strong agreement