LIGHTNING ROUND: DIFFERENTIAL DIAGNOSIS OF DEPRESSIVE STATES
Learning Objectives

• Apply evidence-based strategies to differentially diagnose patients presenting in depressive states with symptoms that resemble depression

• Address specific treatment approaches for different populations with traumatic brain injury (TBI) and associated neuropsychiatric conditions
Depression

• World Health Organization (WHO) recently stated that depression is the leading cause of ill health and disability worldwide

• More than 300 million people

• Increase of 18% between 2005 and 2015
Excessive crying
Excessive laughing

Bipolar Spectrum Disorders
- Elevated mood
- More talkative
- Racing thoughts
- Increased energy
- Decreased need for sleep
- Inflated self-esteem
- Risky behavior
- Impulsivity

Unipolar Depression
- Depressed mood
- Weight loss or gain
- Loss of energy
- Loss of interest in previously enjoyable activities
- Difficulty concentrating
- Excessive sleepiness
- Insomnia

Pseudobulbar Affect

Irritability
Distractibility
Psychomotor agitation
Suicidality

Decreased need for sleep
Risky behavior
Impulsivity

Excessive sleepiness
Loss of interest in previously enjoyable activities
Difficulty concentrating
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Suicidality

Elevated mood
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Suicidality
The Mood Spectrum

- Although categorical classifications may be useful for clinical practice, the overwhelming majority of the evidence points to a dimensional (spectrum) view of mood disorders
  - e.g., treatment response (antidepressant vs. mood stabilizing agent) and links with family history of BP
- Individuals with unipolar depression and "a little bit of mania" are more likely to have an eventual diagnostic conversion to bipolar disorder

So You Think It’s Unipolar Depression?

• Over one-third of unipolar patients are eventually re-diagnosed as bipolar
• As many as 60% of patients with BPII are initially diagnosed as unipolar
• Presence of even subthreshold (hypo)mania symptoms is strongly associated with conversion to bipolar disorder
  • Each (hypo)mania symptom increases risk by ~30%

Clues Across The Spectrum

**Clinical History**
- Family history of bipolar disorder
- Early age at onset of first depressive episode (<25 years)
- # of lifetime affective episodes
- Postpartum depressive episodes
- # of hospitalizations
- Rapid onset of depressive episodes
- Greater severity of depressive episodes

**Treatment History**
- Worse response to antidepressants
- Antidepressant-induced hypomania

**Symptoms**
- Psychotic features
- Atypical depressive symptoms
- Subsyndromal hypomanic symptoms
- Impulsivity
- Aggression
- Hostility
- Comorbid SUD

Depression with Mixed Features (DMX)

• Associated with:
  • Family history of BP
  • Suicidality
  • Antidepressant-induced mania
  • Young age of onset
  • Long duration of illness
  • Poor prognosis
  • Severe depression
  • Antidepressant resistance
  • Females
  • Comorbid anxiety
  • Comorbid SUD
  • Impulse control

The prognosis for depression with co-occurring (hypo)mania (DMX) is much **worse** than for pure unipolar depression or bipolar depression without mixed features.

Symptoms Most Commonly Seen in DMX

- Irritability
- Distractibility
- Psychomotor agitation
- Racing/crowded thoughts
- Increased talkativeness
- Emotional lability
- Rumination
- Initial or middle insomnia
- Dramatic expressions of suffering
- Impulsivity
- Risky behaviors

DMX and Suicidality

• Non-euphoric (hypo)manic symptoms (including psychomotor agitation, impulsivity, irritability, and racing/crowded thoughts) combined with depressive symptoms (i.e., DMX) = recipe for suicidality

• Presence of mixed features increases risk of suicidality by 4X in both unipolar and bipolar depression

• DMX may underlie the connection between antidepressant use and suicidality
  • Most notably in the pediatric population, in which DMX is often the rule rather than the exception
  • Both young age of onset of depression and DMX symptoms suggest higher risk of bipolarity

Pseudobulbar Affect Disorder (PBA)

• Occurs in the context of brain injury, including TBI, stroke, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)
• PBA is characterized by uncontrollable, inappropriate laughing and/or crying
• Patients may experience autonomic changes, increased jaw jerk, exaggerated gag reflex, tongue weakness, dysarthria, dysphagia, and episodic proneness to anger
• Patients with PBA often have:
  • Increased risk of depression and anxiety
  • Decreased quality of life
  • Impaired social interaction (due to embarrassment)

A Rose By Any Other Name Is…Distracting

- Affective lability
- Emotional dyscontrol
- Emotional dysregulation
- Emotional incontinence
- Emotional lability
- Emotionalism
- Excessive emotionality
- Forced laughter or crying
- Inappropriate hilarity
- Involuntary emotional expression disorder
- Labile affect

- Pathological affect
- Pathological laughter and crying
- Pathological weeping
- Pseudobulbar crying

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Need for PBA Guidelines

• Inconsistent use of terminology results in debate and confusion

• Involuntary Emotional Expression Disorder (IEED) is a medically accurate and unifying term

• For differential diagnosis of IEED, most important step is distinguishing crying as part of IEED versus crying in the context of a depressed mood

• In the literature on IEED, a distinction has been made between mood (defined as internal state) and affect (defined as external physical manifestations of emotion)

• This is confounded by labeling some mood disorders (e.g., bipolar, MDD) as affective disorders

Involuntary Emotional Expression Disorder (IEED)

- Core clinical feature of IEED is involuntary outbursts of crying/laughing

- Emotional outbursts have shared common features:
  - Outbursts are stereotyped
  - Mood incongruent, with an intensity out of proportion to the stimulus
  - Episodic, with a return to baseline upon conclusion

- Episodes of IEED may be accompanied by signs of pseudobulbar palsy (PBP): hyperactive jaw, facial reflexes, dysarthria

- Autonomic, respiratory, and vocal changes may occur in IEED

- Bulbar involvement in any disorder is followed by deterioration of the voice, difficulties in phonation, mastication, articulation, and respiration

- Mood changes, especially episodic anger

Symptoms of Disordered Emotional Expression

- Pathological laughing
- Pathological crying
- Labile affect
- Irritability
- Temper
- Disinhibition
- Aggression
- Impulsivity
- Unpredictable and rapidly changing emotions

Potential psychiatric conditions with disordered emotional expression due to dysfunction of the same brain circuits underlying pseudobulbar affect: loss of top-down control of bottom-up emotional drives

- Traumatic brain injury (symptoms of emotional dyscontrol beyond pathological laughing and crying)

- Dementia (neuropsychiatric and behavioral symptoms of dementia, especially agitation, and not just pathological laughing and crying)

- PTSD (symptoms of impulsivity and self-harm)

- Borderline personality disorder (symptoms of impulsivity and self-harm)

- Major depression, depression with mixed features, and bipolar depression, especially treatment-resistant; suicidality

- Miscellaneous impulsive compulsive disorders:
  - Impulsive violence
  - Intermittent explosive disorder
  - Impulsive gambling, binge eating, Internet use
  - Impulsive/compulsive substance abuse
  - Impulsive attention deficit hyperactivity disorder (ADHD)
  - Oppositional defiant disorder (ODD)
  - Disruptive mood dysregulation/ temper tantrums

PBA Registry Series (PRISM) Data

Brooks BR et al. PLOS One 2013;8(8):e72232.

PBA symptom prevalence by CNS-LS threshold.

AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; CNS-LS, Center for Neurologic Study–Laboratory Scale; MS, multiple sclerosis; PBA, pseudobulbar affect; PD, Parkinson’s disease; PRISM, PBA Registry Series; TBI, traumatic brain injury.
PBA Pathophysiology

- Involves neural network of frontal lobes, limbic system, brainstem, cerebellum, or interconnecting white matter tracts of this network.
- Cerebellum appears to play a much greater role than was previously hypothesized.
- Cerebellum - key role in modulating emotional responses, based on input from cerebral cortex.
- Disruption of the corticopontine–cerebellar circuits results in impairment of this cerebellar modulation.
- Variety of neurotransmitters are involved: NE, DA, 5-HT, glutamate, and acetylcholine.
<table>
<thead>
<tr>
<th>Table 2 Diagnostic criteria for pseudobulbar affect</th>
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<tbody>
<tr>
<td><strong>Poeck</strong></td>
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<tr>
<td>The emotional response is situationally inappropriate</td>
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<td>The patient’s feelings and the affective response are not closely related</td>
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<tr>
<td>The duration and severity of the episodes cannot be controlled by the patient</td>
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<tr>
<td>Expression of the emotion does not lead to a feeling of relief</td>
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<tr>
<td><strong>Cummings: necessary elements of the episodes</strong></td>
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<tr>
<td>A change from previous emotional responses</td>
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<tr>
<td>Inconsistent with or disproportionate to mood</td>
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<tr>
<td>Not dependent on a stimulus, or excessive relative to that stimulus</td>
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<tr>
<td>Cause significant distress or social/occupational impairment</td>
</tr>
<tr>
<td>Not accounted for by another psychiatric or neurologic disorder</td>
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<tr>
<td>Not due to a drug</td>
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Treatment Options for PBA

• Antidepressants:
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Tricyclic Antidepressants (TCAs)
• Can help reduce the frequency and severity of PBA episodes
• Typically prescribed at lower doses than for depression
• Dextromethorphan hydrobromide and quinidine sulfate (Neudexta) is the only FDA-approved medication designed specifically to treat PBA

Distinguishing Between PBA and Depression

- PBA is often underrecognized, misdiagnosed, and undertreated
  - Only 40% of individuals who discuss PBA symptoms with a clinician are diagnosed
- PBA is a disorder of affect (the expression of mood), not mood itself
- Often mistaken for depression
  - Duration of PBA episode is shorter (seconds vs. weeks)
  - Crying is not congruent with subjective mood
  - Other symptoms of depression (e.g., fatigue, anhedonia, hopelessness, guilt) are not associated with PBA
  - PBA generally responds faster to pharmacotherapy
- Can be comorbid with major depressive disorder (MDD), making it difficult to diagnose
- Ictal laughing and crying can also be signs of complex partial epilepsy
  - Usually accompanied by alterations in consciousness

Distinguishing Between PBA and Depression

PBA
- Brief episodes (seconds to minutes)
- Sudden, abrupt, no wind down
- Uncontrollable
- Exaggerated reaction or independent of mood

Depression
- Tonic mood (last weeks to months)
- Ongoing sadness or diminished interest
- Crying not well characterized
- Emotional expression matches patient’s mood

Crying
Distinguishing Between Bipolar Disorder and PBA

• PBA may be associated with bipolar disorders, especially with rapid cycling or mixed mood episodes

• Laughing or crying episodes are briefer

• No disturbances between episodes
  • Mood, cognition, and behavior show sustained changes in bipolar disorders

Screening for PBA: CNS-LS

Center for Neurologic Study-Lability Scale (CNS-LS) for pseudobulbar affect (PBA)

The CNS-LS is a short (seven-item), self-administered questionnaire, designed to be completed by the patient, that provides a quantitative measure of the perceived frequency of PBA episodes. The CNS-LS can help physicians accurately diagnose PBA. A CNS-LS score of 13 or higher may suggest PBA.

Patient’s name:

Date of assessment:

Using the scale below, please write the number that describes the degree to which each item applies to you DURING THE PAST WEEK. Write only 1 number for each item.

<table>
<thead>
<tr>
<th>Applies</th>
<th>Applies</th>
<th>Applies</th>
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<tbody>
<tr>
<td>never</td>
<td>rarely</td>
<td>occasionally</td>
<td>frequently</td>
<td>most of the time</td>
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<tr>
<td>1 2 3 4 5</td>
<td></td>
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Assessment questions

1. There are times when I feel fine 1 minute, and then I’ll become fearful the next over something small or for no reason at all.
2. Others have told me that I seem to become amused very easily or that I seem to become amused about things that really aren’t funny.
3. I find myself crying very easily.
4. I find that even when I try to control my laughter, I am often unable to do so.
5. There are times when I won’t be thinking of anything happy or funny at all, but then I’ll suddenly be overcome by funny or happy thoughts.
6. I find that even when I try to control my crying, I am often unable to do so.
7. I find that I am easily overcome by laughter.

Answers

Total Score:

The CNS-LS has been validated in ALS and MS patient populations.

This questionnaire is not intended to substitute for professional medical assessment and advice.

Depression in Patients with Traumatic Brain Injury (TBI)

• Depression is the most common psychiatric complication of TBI

• More than 50% of patients with moderate to severe TBI will experience a depressive episode in the first year post injury

• Patients with TBI remain at elevated risk of depression for decades post-injury

• 90% of patients with TBI and MDD had onset of depression post-TBI, referred to as post-traumatic depression (PTD)

• Patients with mild TBI (mTBI) and depression are more likely to report loss of consciousness at the time of injury

• Depression following TBI is associated with more severe post-concussive symptoms, including headache, blurred vision, dizziness, and memory impairment

• 5X elevated risk of suicide

Post-Traumatic Depression (PTD)

- Adjustment-based depression, may occur rather than biologically-based depression after TBI

- Adjustment-based depression may result from:
  - Pre-injury and comorbid personal factors
  - Changes in functional abilities and community-based participation after injury

- Adjustment-based depression is characterized more by low self-worth, feelings of guilt, agitation, and suicidal endorsement

- Distinct mechanisms for the development of PTD

- Different subtypes of PTD

Juengst et al. Psychology Research and Behavior Management. 2017, 10:175-186
Distinguishing between PTD and MDD

Distinguishing post-traumatic depression (PTD) from MDD:

• PTD characterized more by irritability, anger, and aggression versus sadness or tearfulness

• Most common symptoms of PTD for the first 10 years post-TBI: fatigue, distractibility, and rumination

• Symptoms that best differentiated PTD from MDD: rumination, self-criticism, and guilt

• Depression and TBI share many somatic symptoms: fatigue, poor concentration, and sleep disruption

Juengst et al. Psychology Research and Behavior Management. 2017,10:175-186
Predictors/Etiology of PTD

• Presentation of PTD is a multifactorial response to a number of underlying factors associated with TBI, rather than direct result of a primary pathology

• One challenge is the unique etiology of PTD, which can differ from person to person

• Underlying risk factors for PTD should be identified and managed first, prior to addressing depressive symptoms

• Can maximize potential for positive treatment response

• Apply focused treatments in well-defined subgroups

• For example: recent evidence suggests that fatigue is directly caused by TBI and not PTD

• Most appropriate treatment approach would be to address fatigue first

• First step toward personalized treatment approaches to PTD is to understand the heterogeneity in its risk factors and its underlying causes after TBI

Juengst et al. Psychology Research and Behavior Management. 2017,10:175-186
Biological Mechanisms of PTD: Inflammatory-Induced Depression

- Numerous biological mechanisms through which depression can develop after TBI
- Inflammatory mediators (e.g. cytokines) are elevated with central nervous system (CNS) injury, including TBI
- These markers have been linked to depression in neurologically intact adults and patients with TBI
- Higher acute CSF levels of sVCAM-1, sICAM-1, and sFAS were associated with significant increase in risk for depression 6 months post-TBI
- Higher acute CSF levels of IL-12 were associated with PTD at 12 months
- Inflammation occurring early after TBI may contribute to long-term chronic inflammation, hence chronic risk for depression
- Cytokines, such as IL-6, IL-7, and tumor necrosis factor-α (TNF-α) have been associated with MDD
- Increases in proinflammatory cytokines can result in dampening of brain derived neurotrophic factor (BDNF) expression, which may contribute to depression
- Serum BDNF levels during the first week post-TBI may be indicative of risk for the development of PTD by 1 year

Juengst et al. Psychology Research and Behavior Management. 2017,10:175-186
Traumatic Brain Injury (TBI)

Inflammation
Pro-inflammatory Cytokines (IL-1, IL-6, TNF-α)

Fatigue ↓ interest slowing
IL-7, IL-12, sICAM, sFAS
Mood changes, impulsivity, *Lower BDNF

Malaise w/o known illness → feelings of personal failure and guilt that lead to depression

- Depressed mood
- Lack of interest/decrease in pleasure
- Psychomotor slowing
- Poor concentration
- Anxiety
- Fatigue
- Weight loss

Sickness behavior
- Acute
- Adaptive

Specific symptoms
- Fever
- Malaise
- ↑ Sensitivity to pain

Shared Symptoms
Depression
- Chronic
- Progressive
Specific symptoms
- Suicidal ideation, guilt, low self-worth
- Psychomotor agitation
- Weight gain

Transition from acute, adaptive sickness behavior to chronic, maladaptive depression - Immune dysfunction (autoimmunity, IL-7)

Chronic + Feedback loop

Neuroinflammation
Neurodegeneration

Juengst et al. Psychology Research and Behavior Management. 2017, 10:175-186
Psychosocial Risk Factors for PTD

- Age
- Race
- Less independence in functional tasks after injury
- Engaging in maladaptive coping
- Sleep disturbance or fatigue
- Unemployment of impoverished at time of injury
- Substance abuse before or at the time of injury
- Pre-injury depression or other psychiatric disorder is one of the greatest predictors of PTD

Juengst et al. Psychology Research and Behavior Management. 2017,10:175-186
Treatment for PTD

- Antidepressants have had mixed results in studies of depression after TBI
- May be less effective among individuals with TBI compared to those without
- Reduced treatment effect of SSRIs after TBI may be due to high levels of inflammation post-injury
- Combination therapy: SSRI and anti-inflammatory agent may be promising; further study is needed
- Sertraline may be a promising preventative treatment for PTD
- Behavioral approaches: Metacognitive strategy training, a problem-solving based approach is recommended
- Impairment in problem-solving mechanisms after TBI, which can result in depression
- Treatment should be provided in a top-down manner: focus on functional and activity-based goals rather than improvement of symptoms or bodily functions
- Exercise-based interventions and anti-inflammatory diet show promise
- Future research is needed

Juengst et al. Psychology Research and Behavior Management. 2017,10:175-186
Chronic Traumatic Encephalopathy (CTE)

- CTE is a progressive degenerative disease that results from repetitive head trauma.
- In cases of repetitive mTBIs at least 17% develop CTE.
- Symptoms range from attention/concentration difficulties, to disorientation, depression, memory loss, and dementia.
- Proposed mechanism is “diffuse axonal injury”.
- Characterized by neurofibrillary tangles (NFTs) in frontal and temporal cortices caused by tau prions.
- Atrophy of cerebral hemispheres, medial temporal lobe, thalamus, mammillary bodies, and brainstem, with ventricular dilation and a fenestrated cavum septum pallucidum.
- 50% of brains with NFTs also have diffuse Aβ plaques (30% of these were classic AD neuritic plaques).

Stages of CTE

Four stages of CTE:

1. Depression, headaches, short-term memory loss
2. Difficulty controlling impulses, suicidal thoughts, severe headaches
3. Apathy, severe memory issues, impaired judgment
4. Paranoia, severe depression, aggression, suicidal behaviors

Boston University, 2012
Recent NFL Suicides Attributed to CTE

Dave Duerson 1960-2011
Junior Seau 1969-2012
Ray Easterling 1949-2012
Adrian Robinson 1989-2015
### Depression in Patients with TBI/CTE

<table>
<thead>
<tr>
<th>Medication</th>
<th>Efficacy</th>
<th>Side Effects</th>
<th>Warnings</th>
</tr>
</thead>
</table>
| SSRIs      | • First line of defense  
• Among SSRIs, sertraline has most DA effects | | • Paroxetine may impair cognition due to antimuscarinic properties |
| TCAs       | • Less efficacy than SSRIs | • Higher risk of side effects, especially seizures/cognitive deficits | |
| Bupropion  | • Not recommended | | • Lowers seizure threshold |
| MAOIs      | • Not recommended due to lack of efficacy data | | • Dietary restrictions may be harder to follow in TBI patients |
| Methylphenidate | • Similar efficacy to sertraline  
• Improvement in cognitive deficits | | |

Special Considerations in Patients with TBI: Antidepressants

- Most patients with post-TBI depression do not respond to standard antidepressant therapy
- Depression resulting from a basal ganglia lesion could potentially worsen with antidepressants
- Buproprion and TCAs have an increased risk of seizure associated with them
- Some antidepressants may also interfere with motor function, which may already be compromised in patients with TBI
- Antidepressants with anticholinergic properties (e.g., paroxetine) may further impair cognition

Nonpharmacological Treatment for Depression in Patients with TBI

• Numerous repetitive transcranial magnetic stimulation (rTMS) studies have been performed on patients with MDD

• High-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC)

• Low-frequency rTMS to the right DLPFC

• Recent study: treatment resistant patients with multiple TBIs underwent 20 daily sessions of bilateral rTMS treatment (4000 left-sided excitatory pulses, 1000 right-sided inhibitory pulses)

• Treatment led to improvements in clinician-assessed mood ratings, self-report emotional scores (mood, anger, anxiety and behavioral dyscontrol), fluid cognition, and headaches

• Low-frequency rTMS results in increased levels of brain derived neurotrophic factor (BDNF) in animal models of TBI

Alternative Treatments for Depression in TBI: Methylene Blue

• Methylene blue (MB) for treatment of depression associated with neuroinflammation

• Intravenous MB infusion 15-30 minutes post-TBI reduced cerebral edema, attenuated microglial activation, decreased neuroinflammation, and improved behavioral recovery in TBI mouse model

• Do not use methylene blue if you have used an MAO inhibitor in the last 14 days; a dangerous drug interaction could occur, leading to serious side effects

• Do not use methylene blue if patient is taking an SSRI, especially TCAs

• Warning**Methylene blue is an MAO inhibitor; when taken in combination with SSRIs may result in serotonin toxicity

• Potential interaction effects with other drugs

• Patients with kidney problems should avoid

Alternative Treatments for Depression: Ketamine

- Rapid antidepressant effects in patients with treatment-resistant depression (TRD)
- 24 manuscripts consisting of 416 patients with TRD
- Long-term efficacy of ketamine has not been examined
- Recent studies demonstrate no increase in intracranial pressure (ICP)
- Elevated levels of glutamate immediately after TBI that persist for several weeks
- NMDA antagonist action of ketamine considered neuroprotective

Alternative Treatments for Depression in TBI: Exercise

- Recent studies demonstrate that a physical exercise intervention for patients with TBI results in less depressive symptoms, anxiety, and fatigue
- Improved sleep, community participation, and overall quality of life
- Several studies suggest that physical exercise may alleviate depressive symptoms in TBI populations
- Evidence that stress response is heightened for 2 weeks post-mTBI in animal models
  - Restraint-induced stress significantly elevated CORT and ACTH levels
  - More pronounced and lasted longer than in controls
- 6 weeks of daily or intermittent voluntary wheel-running exercise returns HPA axis to normal response to stress for mild stressors
- 12 weeks of 20-min treadmill running resulted in decreased noradrenaline production during stressful situations

Summary

• Symptoms that are seemingly indicative of major depressive disorder (MDD) may actually be manifestations of a different psychiatric illness

• Some psychiatric disorders most commonly misdiagnosed as MDD are bipolar disorder, post-traumatic depression (PTD) and pseudobulbar affect disorder (PBA)

• Making an accurate differential diagnosis in patients presenting with symptoms of depression is critical to the implementation of optimal patient care