



Mixicity in Depression

What is it?

&

Why is it Important for my practice?

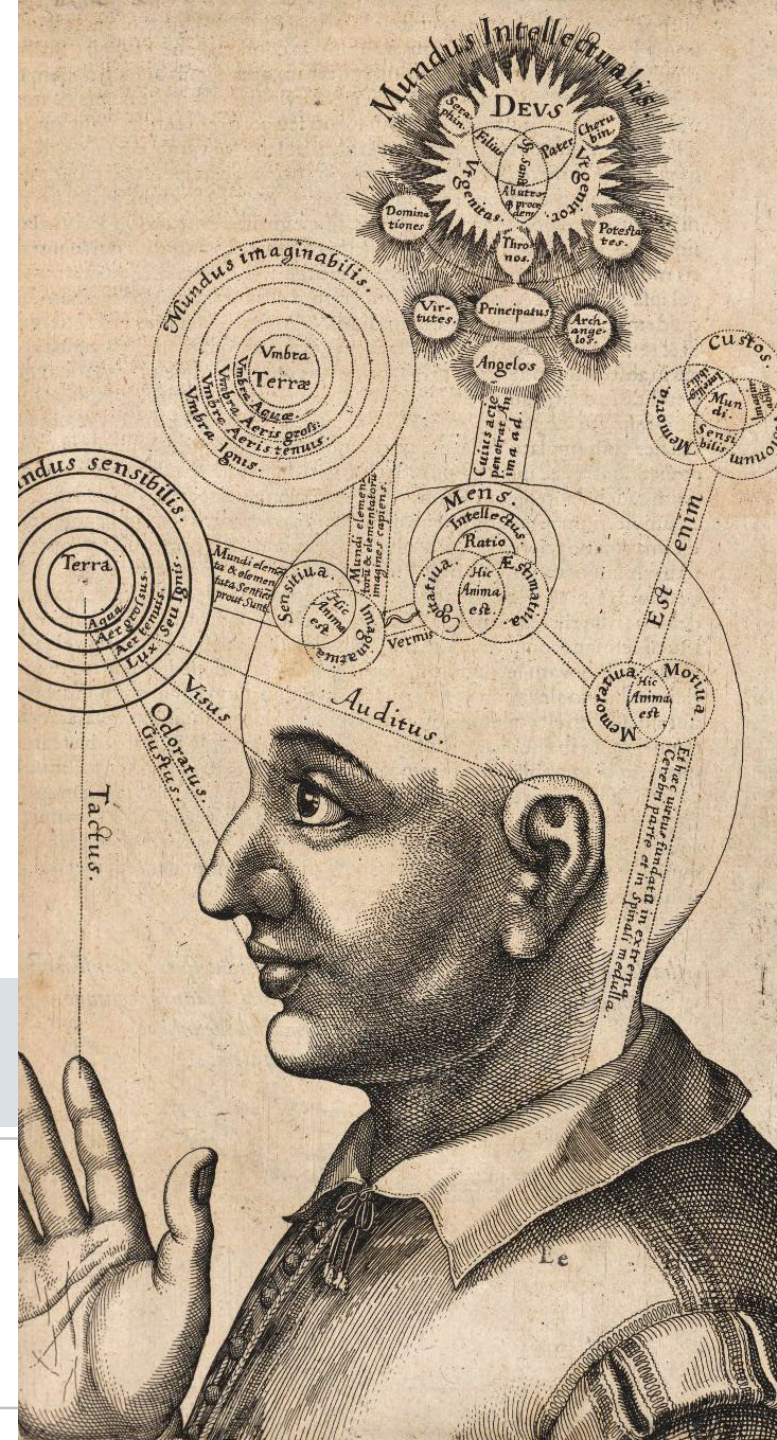
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Objectives

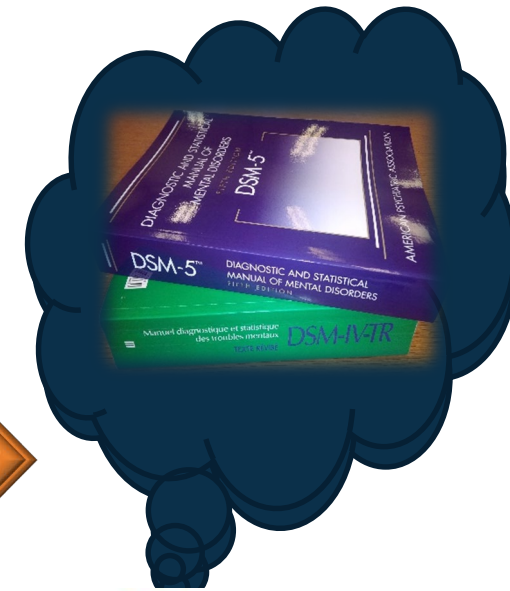
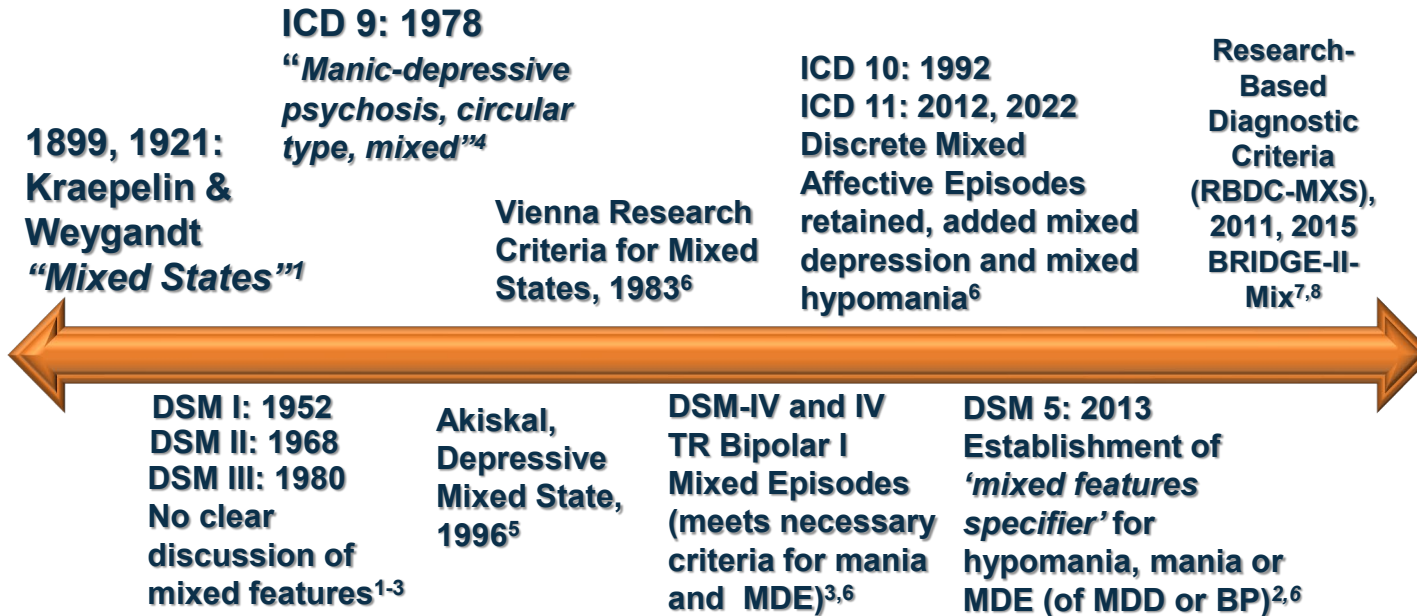
- Review the history of mixed states in depression, focusing on conceptualization, phenomenology, and diagnostic considerations
- Highlight the clinical relevance of correctly identifying/defining mixed states across depression
- Discuss the impact of mixicity on the course of illness and treatment outcome

History & Phenomenology



History of Mixed Features

Timeline for Definitions of Mixed States



- Diagnostic & Statistical Manual=DSM; International Classification of Diseases=ICD; Major Depressive Disorder=MDD; Bipolar=BP
1. Pacchiarotti et al. 2011 Mania and depression. Mixed, not stirred. *J Affective Disorders* 133:105-113.
 2. McIntyre 2017 Mixed features and mixed states in psychiatry: from calculus to geometry. *CNS Spectrums* 22:116-117.
 3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. First edition, 1952; DSM-II,1968; DSM-III 1980; DSM-IV, Text Revision (DSM-IV-TR).2000, Washington, DC: American Psychiatric Association
 4. International Classification of Diseases 1975 Ninth revision.
 5. Akiskal 1996 The Prevalent Clinical Spectrum of Bipolar Disorders: Beyond DSM-IV. *J Clin Psychopharmacol* 16(2):4S-14S.
 6. Maina et al. 2013 The concept of mixed state in bipolar disorder: from Kraepelin to DSM-5. *Journal of Psychopathology* 19:287-295.
 7. Popovic et al. 2015 Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disorders* 17: 795–803.
 8. World Health Organization. (2018). International Classification of Diseases, 11th Revision (ICD-11). Recuperado de <http://www.who.int/classifications/icd/en>.

Emil Kraepelin, 1921

“But then very often we meet temporarily with states which do not exactly correspond either to manic excitement or to depression, but represent a *mixture* of morbid symptoms of both forms of manic-depressive insanity.”

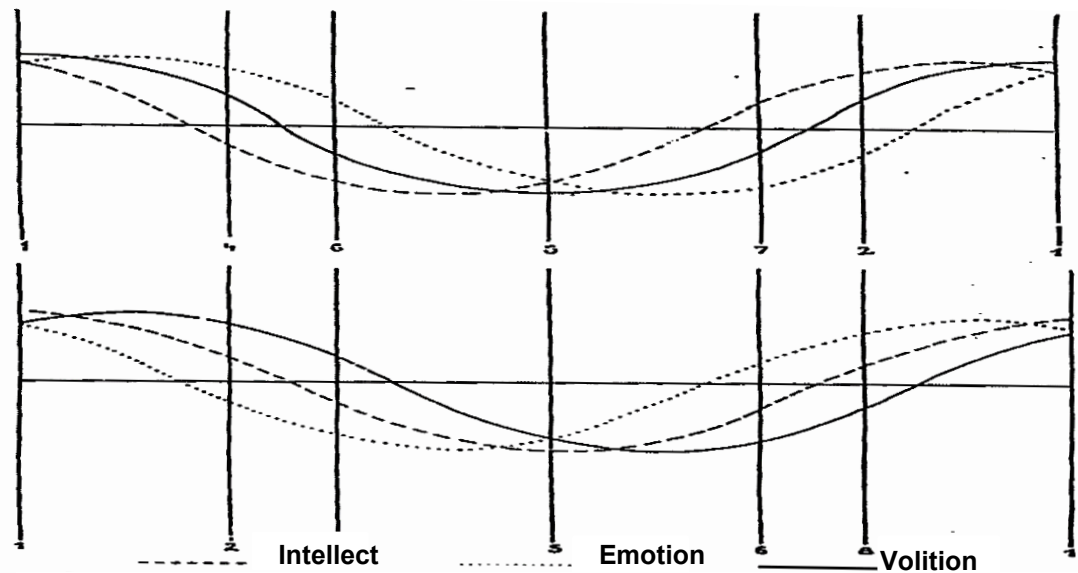


Fig. 20-Comparison of the mixed states of manic-depressive insanity

Prof. Dr. Kraepelin.

Kraepelin, E., 1921. Manic-depressive Insanity and Paranoia. Livingstone, Edinburgh.

Kraepelin's Concept of Mixed States

| | <u>Emotion</u> | <u>Volition/Activity</u> | <u>Thought</u> |
|--------------------------------|----------------|--------------------------|----------------|
| Depression | ↓ | ↓ | ↓ |
| Mania/Hypomania | ↑ | ↑ | ↑ |
| Depressive or Anxious Mania | ↓ | ↑ | ↑ |
| Excited or Agitated Depression | ↓ | ↑ | ↓ |
| Mania w/ Poverty of Thought | ↑ | ↑ | ↓ |
| Manic Stupor | ↑ | ↓ | ↓ |
| Depression w/ Flight of Ideas | ↓ | ↓ | ↑ |
| Inhibited Mania | ↑ | ↓ | ↑ |

Kraepelin, E., 1921. Manic-depressive Illness and Paranoia. Livingstone, Edinburgh.

Kraepelin, DSM-5 and Mixed States

“...we do not see the phenomena of the one state always disappearing at the same time in all the realms of psychic life...”¹

“Rather do some morbid symptoms of the earlier period vanish more quickly, others more slowly, and at the same time some or other phenomena of the state, which is now developing are already emerging”¹

-Kraepelin 1921

“Whereas these concurrent ‘mixed’ symptoms are relatively simultaneous, they may also occur closely juxtaposed in time as a waxing and waning of individuals symptoms of the opposite pole”²

-Glossary of Technical Terms in DSM-5, 2013

Diagnostic & Statistical Manual=DSM

1. Kraepelin, E., 1921. Manic-depressive Illness and Paranoia. Livingstone, Edinburgh.
2. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.

DSM-5 vs ICD-11

- **DSM-5** added “mixed features” specifier to depressions in MDD and Bipolar disorders
 - “*with Mixed Features*” specifier applies when at least three subthreshold symptoms from the opposing pole are present during a mood episode
- **ICD-11** maintains discrete diagnoses for mixed episodes
 - Changes to account for ≥ 3 symptoms of the opposite polarity
 - Different subtypes based on presence or absence of psychotic symptoms

Diagnostic & Statistical Manual=DSM; International Classification of Diseases=ICD

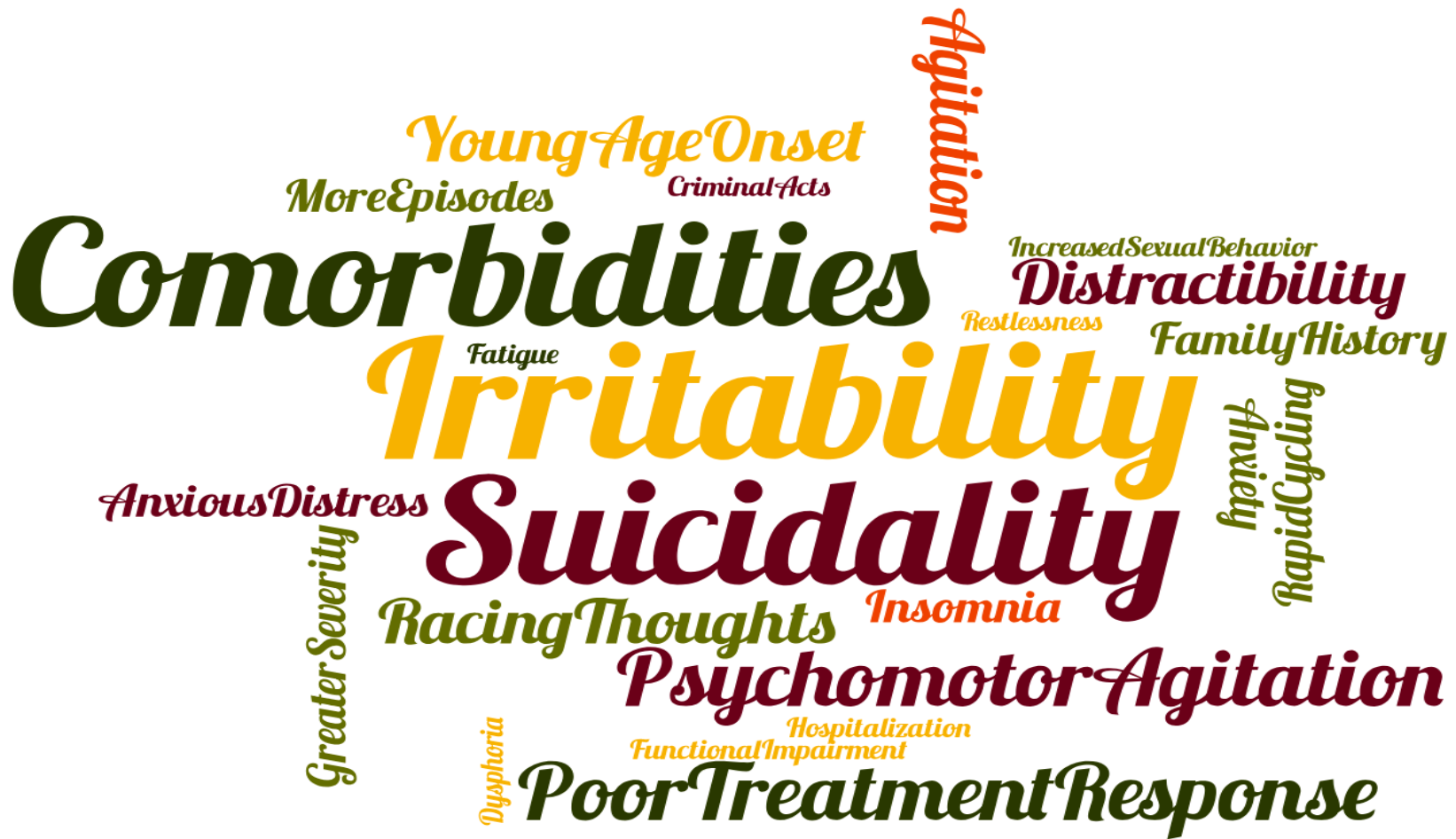
Vieta & Valenti 2013. Mixed states in DSM-5: Implications for clinical care, education, and research. *J Affective Disorders* 148:28–36.

Evidence & Clinical Relevance of Mixicity



Evidence for Mixed Features Symptoms

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Evidence for Mixed Features Symptoms

- Akiskal 1996 The Prevalent Clinical Spectrum of Bipolar Disorders: Beyond DSM-IV. *J Clin Psychopharmacol* 16(2):4S-14S.
- Angst et al. 2010 Major Depressive Disorder with Sub-threshold Bipolarity in the National Comorbidity Survey Replication. *Am J Psychiatry* 167(10): 1194–1201.
- Judd et al. 2012 Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. *J Affective Disorders* 138(3): 440–448.
- Kraepelin, E., 1921. Manic-depressive Illness and Paranoia. Livingstone, Edinburgh.
- Malhi et al. 2014 Are manic symptoms that 'dip' into depression the essence of mixed features? *J Affective Disorders* 192: 104–108.
- Mazzarini et al. 2018 Is recurrence in major depressive disorder related to bipolarity and mixed features? Results from the BRIDGE-II-Mix study. *J Affective Disorders* 229:164–170.
- Pacchiarotti et al. 2011 Mania and depression. Mixed, not stirred. *J Affective Disorders* 133:105-113.
- Pae et al. 2012 Mixed depression: A study of its phenomenology and relation to treatment response. *J Affective Disorders* 136:1059-1061.
- Perugi et al. 2015 Mixed features in patients with a Major Depressive Episode: the BRIDGE-II-MIX Study. *J Clin Psych* 76(3):e351-358.
- Perugi et al. 2019 Patterns of response to antidepressants in major depressive disorder: Drug resistance or worsening of depression are associated with a bipolar diathesis. *European Neuropsychopharmacology* 29: 825–834.
- Popovic et al. 2015 Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disorders* 17: 795–803.
- Shim et al. 2019 The prevalence and diagnostic classification of mixed features in patients with major depressive episodes: A multicenter study based on the DSM-5. *Int J Methods Psychiatr Res.* e1773: 1-8.
- Vieta & Valenti 2013. Mixed states in DSM-5: Implications for clinical care, education, and research. *J Affective Disorders* 148:28–36.
- Zimmerman P et al. 2009 Heterogeneity of DSM-IV Major Depressive Disorder as a Consequence of Subthreshold Bipolarity *Arch Gen Psychiatry* 66(12):1341-1352.

Features Associated with Greater Risk for Emergence of Mixicity

- Past mixed episodes¹
- Increased activation, agitation, irritability, impulsivity, sleep disruption, or suicidality in response to previous antidepressants¹
- Multiple past intolerances to antidepressant treatment trials¹
- Variable clinical presentations within patient¹
- Early onset with multiple episodes^{1,2}
- Past suicide attempts¹⁻³
- Greater comorbidities (i.e., including episodic panic-like symptoms, compulsive behaviors, ADHD symptoms, alcohol and substance use disorders)^{1,2}
- Affective instability and cycling^{1,3}
- Impulsivity^{2,3}
- Family history of bipolarity^{1,2}



1. Mazzarini et al. 2018 Is recurrence in major depressive disorder related to bipolarity and mixed features? Results from the BRIDGE-II-Mix study. *J Affective Disorders* 229:164–170.
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3. Popovic et al. 2015 Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disorders* 17: 795–803.

So What is the Clinical Relevance of Depressive Mixed States?

- Can occur in MDD and BP-II, as well as BP-I^{1,2}
- May be underappreciated by clinicians and mistaken or misdiagnosed³
- More comorbidities including substance use, anxiety symptoms, and cardiovascular disease^{1,3}
- Heightened levels of anxiety and tension³
- Increased suicidality^{2,3}
- May not be readily recognized by using DSM-5 criteria for pure manic and depressive symptoms²
- Common “non-diagnostic” symptoms include irritability, distractibility and agitation³
- Poor response to monotherapy antidepressants⁴
- No treatment indication from FDA, yet¹

Diagnostic & Statistical Manual=DSM; International Classification of Diseases=ICD; Major Depressive Disorder=MDD; Bipolar=BP; Food & Drug Administration=FDA

1. McIntyre et al. 2015 The prevalence and illness characteristics of DSM-5-defined “mixed feature specifier” in adults with major depressive disorder and bipolar disorder: Results from the International Mood Disorders Collaborative Project. *J Affective Disorders* 172: 259-264.
2. Popovic et al. 2015 Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disorders* 17: 795-803.
3. Vieta & Valenti 2013. Mixed states in DSM-5: Implications for clinical care, education, and research. *J Affective Disorders* 148:28-36.
4. Mazzarini et al. 2018 Is recurrence in major depressive disorder related to bipolarity and mixed features? Results from the BRIDGE-II-Mix study. *J Affective Disorders* 229:164-170.

Summary

- Depressive Mixed States are a century-old concept, evolving from Kraepelin's unitary model of manic-depressive insanity
- Conceptualization and recognition still under intense debate internationally, with some arguing that DSM-5 is an inadequate compromise
- Seen in both Bipolar and MDD... *if one attempts to look for them*
- Poorer prognosis
 - course
 - treatment outcome
 - comorbidities
 - suicidality
- Optimal management and treatment strategies require further investigation... stay tuned!

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