Psychotic Disorders: Comorbidity Detection Improves Diagnosis, Treatment and Outcome with Expert Jeffrey Paul Kahn, MD

Katherine Woo, M.D., Eleanor McDaniel, Jeffrey Paul Kahn, M.D., David Puder, M.D.

In this podcast we will interview Jeffrey Paul Kahn, MD, a psychiatrist who recently co-edited a book called *Psychotic Disorders: Comorbidity Detection Promotes Improved Diagnosis and Treatment*. Our focus will be on different presentations of psychosis and how through a good history you can better treat the underlying issue and choose optimal treatments. Dr. Kahn completed medical school, psychiatry residency and fellowship at Columbia University, and is now a Clinical Professor of Psychiatry at Cornell. In addition to this recent book on psychosis, he has done extensive work with other books, book chapters and publications on topics such as occupational psychiatry, anxiety, and heart disease. He authored a book on an evolutionary theory that anxiety and depressive disorders evolved from primeval altruistic instincts. He and Katherine Woo have no conflicts of interest.

During this episode, we will focus on the five different subtypes of psychosis:

1. Obsessive-compulsive schizophrenia
2. Panic-psychosis: schizophrenia with comorbid panic disorder
3. Persecutory delusional disorder and social anxiety
4. Delusional depression and melancholia
5. Atypical depression and bipolar I manic delusions

Although the book mentions two other types, we will not review them in this episode:

6. Substance use psychosis
7. Iatrogenic and medical-illness-related psychosis

This PDF is a supplement to the podcast “Psychiatry & Psychotherapy” **Episode 117** found on **iTunes**, **Google Play**, **Stitcher**, **Overcast**, **PlayerFM**, **PodBean**, **TuneIn**, **Podtail**, **Blubrry**, **Podfanatic**

What is Psychosis?

- Psychosis is a clinical category with various symptoms that are diagnosed by clinical manifestations rather than with laboratory data, genetics, or neuroimaging.

- Typical psychotic symptoms include delusions, hallucinations, disorganized speech/behavior. Other psychotic symptoms seen in nonpsychotic patients include neologisms, thought blocking, other thought disturbances, and negative symptoms.

- Psychosis is commonly thought of as being associated with schizophrenia, but it only encompasses 30% of the psychotic spectrum. What about the other 70%? Psychosis is a

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heterogeneous disorder and its symptoms lie on a spectrum. It can vary in presentation/severity among patients and be seen to overlap in various psychiatric illnesses.

- Patients with schizophrenia often have other psychiatric comorbidities including anxiety and depression, more so than the general population.
  - Do these comorbidities exist as a result of schizophrenia or does the presence of these symptoms make a person more prone to psychosis?
- In turn, people with non-psychotic disorders can present with a multitude of symptoms, including symptoms mimicking psychosis.

Do the common theories for psychosis actually reflect psychosis-proneness rather than specific psychoses?

- DA dysfunction theory
  - Increased dopaminergic activity may cause an increase in psychosis susceptibility.
  - DA is responsible for increasing pleasure and appetite as well as fear and anger. Intense DA activation can thus stimulate our primeval social instincts, and overwhelming our rational conscious thoughts as a result.
  - Increased dopaminergic activity is seen in schizophrenia, those prone to developing schizophrenia, as well as those with psychotic symptoms.

- Hypofrontality theory
  - Thinning of the frontal cortex and differing neuronal structures are seen in people with psychosis along with people at high risk of developing schizophrenia.
  - Genetic factors can increase risk hypofrontality.
  - Impairs conscious thought reduces attention span and impedes processing of social cues
    - Russell et al., 2006, conducted a study that used microexpression training to treat a group of people with schizophrenia, as well as a control group, to assess the possibility of emotional recognition remediation. In terms of the emotion-matching task, the schizophrenia group improved to the level of pre-trained controls through the training. Check your ability to read microexpression: here.

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        - *Botox Block of Microexpression*
            - With mirror neurons, a person is able to see someone's emotions and mirror them in their own facial expressions.
            - With botox, you are blocking someone's ability to connect with people because you are paralyzing their ability to use microexpressions to mirror emotion.
                - Unable to show anger, disgust, and sadness or see them in other people.
            - In psychotic disorders, emotion recognition might be slowed by impaired frontal lobe processing of mirrored expressions.
    - Is psychosis an imbalance between consciousness and socially-instinctive emotions that leads to the mental emergence of unmoderated instinctive fears?

- Neurodevelopmental theory
    - Prenatal/perinatal events can increase risk of psychosis in life as well as the cognitive impairments seen in schizophrenia.
    - Biological risk and genetics make a person more prone to psychosis and also affect how that person responds to significant events/trauma.
        - In a prior episode, we talked about BPD heritability was estimated at 46% (95% CI = 39–53) and the remaining variance was explained by environmental factors.
        - Height
            - Heritability: 89-93% (Silventoinen, 2003)
        - ADHD
            - Heritability: 71-73% (Nikolas, 2010)
        - Schizophrenia
            - Heritability: 73%
            - Concordance rates: 33% MZ twins and 7% in DZ twins (Hilker, 2018)
        - Bipolar
            - Heritability: 60% (Johansson, 2019)
    - Developmental risk-factor model:
        - Stress can increase DA dysregulation, which then causes psychotic experiences, which adds more stress, which then leads to more DA release.

How do you test someone who is psychotic?

- Look for the hints of comorbidity: first is prior history and second is common characteristics associated with specific comorbidities.

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- For most accurate results, it is best to wait until the patient is in a stable state and from there a more thorough interview can be conducted.
- By working with and treating the comorbidities, there is an incidental effect on the psychosis.

Which anxiety and depressive subtypes can precede psychosis in psychosis-prone people?

Five Psychosis Subtypes

1. OCD
2. Panic disorder
3. Social anxiety
4. Melancholic depression
5. Atypical depression

1. OCD

What is obsessive-compulsive schizophrenia (OC-SCZ)?

- Similarities between OCD and schizophrenia:
    - Prevalence (2-3%), age of onset (2nd-3rd decade, earlier OC onset than SCZ, particularly in males), course of illness (chronic, fluctuating), structural/functional brain abnormalities and involvement of neurotransmitters (DA, 5-HT, glutamate).
    - Symptoms:
        - How do you differentiate between obsessions vs. delusions?
            - Some people with OCD present with unusual or bizarre obsessions, which may cloud the distinction between an obsession vs. delusion. Ex: compulsive hand washing +/- command auditory hallucinations, ego-dystonic obsessions as thought insertions/auditory hallucinations.
                - Four pathologic dimensions seen in OC-SCZ:
                    - Forbidden thoughts - aggressive or sexual
                    - Symmetry obsessions and ordering compulsions
                    - Contamination obsessions and cleaning compulsions
                    - Hoarding obsessions and checking/repeating compulsions
        - Affective symptoms

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        - Patients with schizophrenia with comorbid OC symptoms have more severe depressive symptoms and higher rates of suicidality.
    - OCD-related pathologic slowness/doubt vs. schizophrenic ambivalence
    - Lack of insight
        - Significant subset of patients with OCD have poor insight into their condition. DSM-5 recognizes this by indicating identifiers (OCD with good/fair insight, with poor insight, with absent insight/delusional beliefs).
        - Majority of patients with OC-SCZ have fair insight into their OC symptoms; however, during psychotic breaks, their obsessions may interlace with psychotic symptoms, making it difficult to differentiate the two.

- Differences:
    - Symptoms specific to schizophrenia include negative symptoms, disorganized thought, hallucinations.

- Numerous epidemiological studies have shown a clear relationship between OCD and schizophrenia.
    - Meta-analysis of 34 studies with >3000 participants estimated 12.1% prevalence of OCD in schizophrenia, compared to 1-2% in the general population.
    - Presence of OC symptoms was associated with higher global, positive, and negative symptoms.
    - A study based on Danish registries revealed that prior diagnosis of OCD was associated with an increased risk of developing schizophrenia (incidence rate ratio (IRR) = 6.9; 95% CI, 6.25-7.60) and schizophrenia spectrum disorders (IRR = 5.77; 95% CI, 5.33-6.22) later in life. Children of parents with OCD had an increased risk of schizophrenia (IRR = 3.10; 95% CI, 2.17-4.27).
    - A Swedish registry-based longitudinal cohort study found that patients with OCD had a substantially higher risk of having a comorbid diagnosis of schizophrenia and schizoaffective disorder compared with individuals without OCD.
    - Individuals diagnosed with OCD had 3x higher risk of receiving a later diagnosis of schizophrenia compared with individuals without OCD.
    - Patients diagnosed with schizophrenia had 7x higher risk of later being diagnosed with OCD, and those with schizoaffective disorder had 5x higher risk.
    - An Australian study showed higher risk of schizophrenia in the OCD group compared to matched non-OCD controls (HR 30.29, 95% CI, 17.91-51.21).

- Treatment:

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- Mono therapy with an atypical antipsychotic. *Atypical antipsychotics may actually induce OC symptoms due to their anti-serotonergic/dopaminergic effects.
  - But some studies have shown olanzapine or aripiprazole to be effective in treating both OC and schizophrenia symptoms.
    - DJP: Interesting- I had a patient with both OCD and schizoaffective disorder and zyprexa and anafranil were his life-saving meds.
- Antipsychotic (AP) + SSRI
  - Adjunct SSRIs may help. Dose may be similar to ordinary OCD dose, but sometimes poorly tolerated.
  - Escitalopram (10-40mg/day) + AP showed effectiveness in treating OC-SCZ.
  - Fluvoxamine (100-200mg/day) also showed potential, but may cause increased impulsivity and aggressiveness.
  - A few antidotal cases suggest that fixed-dose Q12H clonazepam may diminish agitation or psychosis caused by high dose SSRIs in OCD-SZ.
  - Important to consider drug-drug interactions between AP and SSRI.

- Non-pharmacologic treatments
  - CBT effectiveness unclear in OC-SCZ. May cause psychotic relapse due to increased stress during therapy.
  - DJP: My experience was that empathy and maintaining the therapeutic alliance was key. Sometimes just keeping them on meds is tough.
  - Small number of cases can use dynamic psychotherapy in their later stages of treatment.

- Key points:
  - It is important to recognize that the diagnosis of non-psychotic OCD in a patient may be a risk factor for schizophrenia later in life, or may even coexist as a unique entity, namely OC-SCZ, as discussed above. Thus, take a thorough history (including family history of SCZ) prior to starting an SSRI for treatment of OCD, as misdiagnosis can lead to psychosis.
  - Atypical antipsychotics may cause OC symptoms or exacerbate preexisting OC symptoms.
  - Patients with schizophrenia who are routinely evaluated for OC symptoms must be presented with carefully-phrased questions, as it may be difficult to distinguish between psychotic symptoms of OC symptoms in these patients.
  - Assess for suicidal ideation/plan in OC-SCZ patients.
  - Evaluate for other OCD-related disorders (body dysmorphic disorder, hypochondriasis, tic disorders, and eating disorders) in OC-SCZ, as they tend to have higher incidence of comorbid disorders related to OCD.

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    - Future studies to help better delineate subsets within OC-SCZ: schizophrenia with OC symptoms vs. OCD with poor insight/psychotic features

- Example: A 60-year-old woman who had OCD since childhood, and psychotic OCD since her twenties. She lived in her apartment with the windows painted black and the door always closed. She only wore white and never drank tap water because she did not want any impurities.
    - Presumably, her OCD interacted with underlying psychosis susceptibility.
    - Achieved remission of both her OCD and psychotic symptoms with antipsychotic + high dose SSRI + Q12H clonazepam

2. Panic Disorder

What is panic psychosis?

- There is high prevalence of panic anxiety in patients with schizophrenia: up to 45% according to Epidemiological Catchment Area study and 100% in a small carbon dioxide panic challenge study of patients with schizophrenia with voices, confirmed by a structured interview.
    - Panic-schizophrenics have an earlier age of onset, increased severity of symptoms and disease course, more positive symptoms/paranoia/suicidality, and lower quality of life.

- Patients with panic disorder without psychosis have a higher incidence of ideas of reference and paranoid ideation compared to normal controls without panic.

- Reduced GABA activity = increased anxiety. Those with panic disorder have decreased GABA levels in the prefrontal cortex as well as dysfunctional GABRA5 and GABRB3 genes.
    - Schizophrenics also have decreased GABA levels in the prefrontal cortex.
    - Use of adjunctive clonazepam (fixed dose Q12H, but not other benzos) can be highly beneficial in treating patients with comorbid panic and schizophrenia, and may contribute to psychosis reduction. Clinical experience and some published reports support this treatment, but large scale controlled studies are still needed.

- Panic-schizophrenia can have panic symptoms that present in psychotic form (ex. paroxysmal auditory hallucinations with concurrent panic anxiety symptoms), making it difficult to delineate underlying panic disorder during psychosis. A specialized structured interview, *The Panic and Schizophrenia Interview* (in book), has shown panic concurrent with voices in virtually all patients in two studies.

- Treatment

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- Consider initial fixed dose q12h clonazepam (not other benzos) + antipsychotics + psychotherapy
- Q12H clonazepam has been seen to cause significant resolution of auditory hallucinations, reduced positive/negative symptoms, improved cognitive function, and reduced AP dosage requirements.
  - Weigh risks/benefits of benzo use
    - Less debate now on risks of cognitive impairment and dementia with benzo use
      - Associations of Benzodiazepines, Z-Drugs, and Other Anxiolytics With Subsequent Dementia in Patients With Affective Disorders: A Nationwide Cohort and Nested Case-Control Study https://pubmed.ncbi.nlm.nih.gov/32252539/
        - 171,287 patients diagnosed with affective disorder between 1996 and 2015, with any use of benzo or Z-drugs, followed for ~6years.
        - No association between benzo/Z-drug use and subsequent dementia. Possible protective effect.
      - Do benzos cause Alzheimer's disease? https://pubmed.ncbi.nlm.nih.gov/32475136/
        - Benzo use may affect some recent recall, reversible upon discontinuation. It may not actually cause dementia.
        - It is plausible that untreated anxiety disorders may increase dementia risk, perhaps slowed by proper treatment.
- Use of SSRI helps with decreasing panic but the psychosis persists, possibly because they have a different (non-GABA) anti-panic mechanism.

- Key points:
  - Screen for panic anxiety, preferably after stabilization of acute psychosis.
  - Ask about auditory hallucinations: are they constant or do they intermittently occur abruptly, with associated panic symptoms?
  - An effective tool for diagnosing panic disorder in schizophrenic patients: Panic and Schizophrenia Interview (PaSI) – Dr. Jeffrey Kahn
    - May be difficult to diagnose in these pts due to impaired cognition, poor cooperation, paranoia.

3. Social Anxiety

Is persecutory/paranoid delusional disorder a psychotic form of social anxiety disorder?

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- Delusional disorder, persecutory type
    - Central theme of the delusion involves the individual's belief that he/she is being conspired against, cheated, spied on, followed, poisoned or drugged, maliciously maligned, harassed, or obstructed in the pursuit of long-term goals.
    - Persecutory delusional disorder (PDD) is frequently misdiagnosed as schizophrenia.
        - Unlike schizophrenia, psychotic patients with sole persecutory delusional disorder do not have hallucinations and do not have marked decline in psychosocial functioning.
        - Paranoid delusions are commonly seen in patients on the schizophrenia spectrum, thus making distinction between the persecutory delusional disorder vs schizophrenia difficult.
            - Psychotic patients with sole persecutory delusional disorder usually do not have insight into their condition, decline all treatment, experience social isolation but do retain a great deal of functional activity. This differs from the negative symptoms of schizophrenia.

- Social anxiety disorder (SAD)
    - Prevalence is ~6.8% in 12 months.
    - Onset at young age (12-17 y/o), chronic course (>10 years), W > M, associated with childhood trauma. Usually present with other comorbid psychiatric disorders including schizophrenia.
    - Patients with SAD often isolate themselves due to fear of embarrassment, rejection, judgement from others. This can make diagnosis of SAD vs. schizophrenia spectrum d/o difficult.
    - Paranoid feelings can arise in non-psychotic social anxiety patients, with persistent thoughts that they are being judged negatively. Can even progress to full on psychosis if paranoia becomes severe, and if psychotogenic factors are present. Persecutory delusional disorder and SAD share common cognitive processes including ideas of reference (the belief that occurrences or details in the world relate directly to oneself).
        - Psychotic manifestations of SAD can occur due to:
            - Hypofrontality limiting ability to evaluate internal fears Increased stressors/traumatic experiences, and other psychotogenic factors
            - Underlying concern about authority figures associated with ordinary SAD

- SAD is a common comorbid disorder in patients with schizophrenia (17%).
    - Associated with increased suicidality, lower quality of life, impaired social functioning, low self-esteem.
    - Presence of SAD leads to earlier disease onset and poor prognosis.

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    - Low self-esteem -> increased paranoia -> paranoid/persecutory delusions

- Some patients with SAD can develop persecutory delusional disorder later in life (psychotic social anxiety disorder?).
    - Reduced frontal cortex hypofrontality -> exaggerated amygdala reactivity -> delusions
    - Reduced conscious modulation of hypofrontality + adverse events -> delusions

- People that have non-psychotic social phobia go one of two directions:
    - Avoiding public interactions, such as public speaking, that would cause them anxiety.
    - Counterphobia, where they jump into situations that go against what feels comfortable in an attempt to conquer their fear.
        - Many performers have this, which allows them to be more aware with live audiences.
        - They work much harder so they can avoid embarrassment.

- Treatment
    - SAD + PDD
        - antipsychotic + SSRI + psychotherapy
            - Fluoxetine is long acting, in this potentially noncompliant group
            - Ex: Aripiprazole is a neuroleptic that also acts as an SSRI booster

- Key Points:
    - When assessing pts for SAD vs. PDD ask yourself, “Is this an exacerbation of SAD symptoms or a true underlying psychotic disorder? Does the patient have insight?”
        - Childhood trauma history, early symptoms of excessive shyness, SI/HI, access to weapons
    - Screening tools: Liebowitz Social Anxiety Scale (LSAS)

4. Delusional (Psychotic) Depression

Do melancholic depression and psychosis exist on a continuum? Maybe melancholic depression and delusional depression should be distinct diagnoses rather than subtypes of depression (DSM-5)?

- Psychotic features are present in 14% to 25% of patients with MDD.
    - Usually consist of delusional beliefs of worthlessness, excessive guilt, idea that their body is rotting or even dead (Cotard’s).
    - Psychotic depression is a severe form of MDD with melancholic features.

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        - Melancholia = partial insanity with delusions, often with extreme pessimism, anhedonia, hopelessness
            - Often has an acute onset, resolves within 12 months, recurrent, more common in elderly & recently retired men.
            - Differences from non-melancholic depression:
                - Psychomotor retardation, pervasive sad mood, nonreactive mood, vegetative dysfunction (appetite, sleep), anhedonia, delusional symptoms (not required but often present)
                    - Common delusions are nihilistic in nature, with feelings of hopelessness, worthlessness, guilt, sin.
                - Associated with long allele of 5-HT transporter gene, altered signal transduction in fibroblasts, reduction in hippocampal volume, less gray matter volume in left posterior insula, more white matter volume in upper brainstem tegmentum, increased rate of dexamethasone non-suppression (high cortisol on dexamethasone suppression test), reduced REM latency and sleep duration.

- Development of psychotic symptoms during a depressive episode as well as development of depression during a psychotic episode are both common.
    - Depressive episodes occur rather frequently in schizophrenic patients, regardless of the stage of their illness.
        - Research shows that 10% of schizophrenics commit suicide, of which 60% are associated with depressive symptoms.
        - These patients may appear emotionless, however, have significant internal delusions -> masked delusional depression.

- Treatment
    - Neuroleptic + antidepressant is usual medication approach
    - Patients with psychotic depression and melancholic depression respond better to TCAs than SSRIs. Psychotherapy is less effective in these subsets of depressed patients.
    - Can also consider ECT as first-line.
    - Consider prophylaxis with antidepressant for recurrent episodes.
    - Consider short-term benzodiazepine use for initial reduction of anxiety, insomnia, and pessimism.

- Key Points:
    - Important to take a thorough history. Ask about life events, recent stressors, and any medical issues that may be contributing to symptoms of depression.

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        - Labs to consider: CBC, fasting glucose, electrolytes, autoimmune Abs, HIV, syphilis serology, BUN/Cr, LFTs, TSH
        - Head imaging
        - Assess for delirium
    - Avoid open-ended questions, focus on specific/direct questions, and avoid prolonged silences.
    - Start with positive topics first to avoid causing too much discomfort in these patients who often have poor self-esteem.
    - Screening tools: Psychotic Depression Assessment Scale (PDAS), Brief Psychiatric Rating Subscale (BPRS-5), Calgary Depression Scale for Schizophrenia (CDSS)
    - Assess for suicide risk. Patients with delusional depression have an increased risk of suicide attempts.

5. Atypical Depression (MDD with atypical features)

What is the most common type of depression seen with bipolar spectrum disorders?

- Unlike typical depression, symptoms include mood reactivity, hyperphagia, hypersomnia, rejection sensitivity.

- Prevalence of 15.7% to 43% in depressed patients, more common in younger women.

- Common comorbidities include panic anxiety, social anxiety, eating disorders, substance-related disorders, somatization disorder.

- Most common type of depression seen in bipolar I disorder
    - Conversely, patients with atypical depression are more likely to have a bipolar I manic episode and have higher rates of comorbid bipolar I disorder than depressed patients without atypical features.

- Link between bipolar I and atypical depression?
    - Both disorders are associated with serotonergic changes, and with circadian rhythm genes.
    - Evolutionary theory of bipolar I origins
        - Atypical depression = hibernation
        - Bipolar I mania = exaggeration of awakening from hibernation
    - Shorter days during winter months exacerbate atypical depression while longer days during spring and summer months are associated with new onset bipolar mania.

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- Atypical depression is also associated with personality disorders (avoidant, borderline, histrionic), all of which reflect different ways of coping with rejection sensitivity and mood reactivity seen in atypical depression.
    - In patients with comorbid atypical depression and personality disorder, diagnosis of atypical depression may be missed due to their symptoms being solely attributed to personality disorder.

- Treatment
    - For those with comorbid bipolar I and atypical depression, consider anti-manic + antipsychotic + antidepressant.
        - Weigh the risks/benefit of antidepressant use, as it can potentially trigger mania. Is atypical depression part of the bipolar spectrum?

            - SSRIs have the lowest risk of manic conversion among antidepressants.
            - Beneficial for acute and chronic bipolar depression
            - SSRI Boosters (mostly 5-HT agonists): buspirone, lithium, trazodone; all in low doses
            - Aripiprazole (neuroleptic side effect concerns)
            - Rexulti (neuroleptic side effect concerns)

    - **Light therapy** for atypical depression is well known; various dark therapies reported as useful adjuncts for acute mania in bipolar disorder.

- Key Points
    - Screen for atypical depression in bipolar patients, preferentially after treatment of acute mania.
    - Atypical depression is associated with bipolar disorder and personality disorders.

        - In those with comorbid personality disorder, atypical depression is often missed. Symptoms may be attributed to their personality, especially in borderline PD, as it can often present with psychotic symptoms.

Maybe melancholia and atypical depression should be separated from the umbrella of major depression disorder.

- They are currently subtypes of the overarching major depression disorder but many believe they are distinctly different.
    - Max Fink's book on Melancholia
    - Donald Klein uses the argument of pharmacological dissection.

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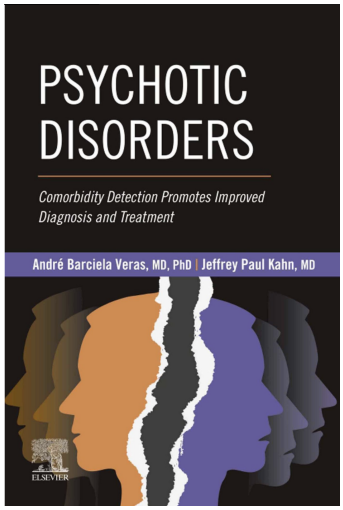
- The different responses to psychoactive drugs shows a difference in the condition.
- All antidepressants will treat melancholia but not all of them will treat atypical depression.

Book Covered In This Episode:



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Osler M, Jorgensen MB. Associations of Benzodiazepines, Z-Drugs, and Other Anxiolytics With Subsequent Dementia in Patients With Affective Disorders: A Nationwide Cohort and Nested Case-Control Study. Am J Psychiatry. 2020 Jun 1;177(6):497-505. doi: 10.1176/appi.ajp.2019.19030315. Epub 2020 Apr 7. PMID: 32252539.

Private practice:

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Mentioned:
Max Fink Melancholia book.

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