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The Case: Achieving remission with medication management augmented with pet therapy

The Question: Do avoidant symptoms respond to medication management?

The Dilemma: Psychotherapy may not alleviate personality traits

Pretest self-assessment question (answer at the end of the case)

Which antidepressant monotherapy most mimics the classic two-drug augmentation strategy where a partial selective serotonin reuptake inhibitor (SSRI) responder has the anxiolytic buspirone (BuSpar) added in an adjunctive manner?

A. Vilazodone (Viibryd)
B. Mirtazapine (Remeron)
C. Aripiprazole (Abilify)
D. Nefazodone (Serzone)
E. Vortioxetine (Brintellix)

Patient evaluation on intake

- 51-year-old woman states that she "doesn't care anymore"
- She has "fought her way off alcohol and out of the housing shelter and people are still not very nice"
- "Alcoholism took away my things" and she "is struggling to get them back"

Psychiatric history

- Patient had been without major psychiatric symptoms until she was in her 30s
- Was gainfully employed as an office manager but began to drink alcohol as stress at work and home mounted
  - Became a daily drinker with clear tolerance to increasing amounts of alcohol, and a failure to fulfill social roles and obligations as a result
  - Lost her job and her family, then became homeless and lived in a shelter
  - Attended Alcoholics Anonymous (AA) and became sober
    - Now, has been sober for at least 10 years
- However, she has not been able to return to gainful employment due to depression and anxiety
  - Works intermittently and volunteers at some local events
  - Prefers to meet and befriend people who will automatically accept her and not reject her
  - Often is very sensitive to criticism

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  - These efforts are often thwarted as the patient frequently becomes dysphoric and isolative, but then blames others for not checking on her, helping her, or caring about her
  - This dynamic sets up more depression and anxiety as a result
- She admits to full major depressive disorder (MDD) symptoms
  - She has passive suicidal thoughts only in that she "doesn't care if she were to die in her sleep as she wouldn't mind"
  - Denies guilt/worthlessness symptoms but is often agitated
  - Poor concentration, low energy, and amotivation are evident
  - Mood is constricted and often dysphoric
- Additionally, she "worries about everything" all the time, cannot focus, and is tense
  - Feels she was like this before the alcohol use disorder (AUD) and MDD started
  - These worry symptoms get worse when the MDD escalates
  - Admits that her drinking lowered this type of anxiety effectively
- There is no evidence of psychosis, mania, other anxiety, or other substance use disorder (SUD)
- She has relatively few friends but has strong but tenuous family ties in the region
  - Feels overly criticized, judged, or put down, which causes her to isolate herself more and become depressed

Social and personal history

- Graduated high school and worked successfully as an office manager for many years
- Married and is divorced and single now
- Now is estranged from her grown daughter
- Does not use drugs or alcohol and has been sober for more than 10 years

Medical history

- Osteoporosis with falls and fractures
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Essential familial tremor

Family history

- The patient admits a family history of
  - MDD in sister
  - GAD in sister and an aunt
  - AUD throughout extended family

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Medication history

- Very few treatments were given with the previous provider, who utilized mostly low-dose selective serotonin reuptake inhibitor (SSRI) antidepressants, and focused more on weekly psychodynamic psychotherapy (PDP) as the treatment of choice with an area therapist
- Currently, perhaps 20% global improvement in intensity and duration of depressive symptoms at most is noted, but still has issues with generalized anxiety disorder (GAD) and avoidant traits after two years of weekly PDP

Psychotherapy history

- Two years of weekly PDP
- Several years of supportive psychotherapy prior
- Regular use of 12-step AA groups
- Small, unsustained responses to these psychotherapeutic interventions outside maintenance of full sobriety are noticed

Patient evaluation on initial visit

- Gradual onset of MDD symptoms after sobriety achieved
- Mounting social stressors regarding finances, housing, and family issues were the likely triggering set of events
- This is associated with a premorbid GAD and avoidant personality traits
  - Patient admits difficulty making and maintaining friendships
  - She will often only approach others if guaranteed of being liked or accepted
  - When stressed or depressed, she will often isolate herself and become interpersonally detached
  - This makes it hard for her to re-engage her friendships, leaving her feeling more alone, abandoned, and angry
    - Two years of psychotherapy have only minimally lessened this maladaptive set of traits
- MDD is moderate; she is not suicidal
- She has been compliant with medication management and psychotherapy sessions
  - Reports no current side effects
- She has good insight into her anxious-depressive symptoms but not her avoidant patterns

Current medications

- Sertraline (Zoloft) 100 mg/d (SSRI)

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Question

In your clinical experience, do patients with avoidant personality traits or disorder respond to antidepressants?

- Yes
- No
- Sometimes

Attending physician's mental notes: initial evaluation

- This patient has chronic MDD
- When MDD is in remission, she seems to be left with anxiety and avoidant traits
  - These residual symptoms predispose her to more stress and resultant major depressive episodes (MDEs)
- She has not seen full remission of *all* psychiatric symptoms in last 10 years
- She does function relatively well with regard to activities of daily living and has reasonable social support
- Her initial failure currently to a moderate-dose of SSRI is not alarming as only about one-third of patients remit on initial treatment
  - However, she likely has failed with two to three SSRIs now, at varying doses at a multitude of previous providers
- She seems to be failing to respond to a reasonable course of psychotherapy
- She is solidly sober, compliant, verbal, and engaging, which helps her prognosis

Question

Which of the following would be your next step?

- Increase the sertraline (Zoloft) to the full approved dose of 200 mg
- Switch to a non-SSRI as she has failed this antidepressant mechanism of action repeatedly
- Augment the current SSRI with another agent to increase response
- Combine the current SSRI with a second antidepressant to increase response
- Do nothing additionally outside continuing PDP
- Change from a PDP approach to either interpersonal psychotherapy (IPT) or cognitive behavioral psychotherapy (CBT)

Attending physician's mental notes: initial evaluation (continued)

- This patient seems to be on the gold standard approach to treating MDD but being on a few SSRIs in a row makes little sense and likely offers little hope for remission

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- Her prognosis seems fair in that she is relatively undertreated with regard to antidepressant trials
  - However, there is concern that her avoidant traits have been addressed for two years with minimal insight and reduction of these behaviors
- She does meet criteria for MDD, GAD, AUD in full sustained remission, and likely, a Cluster C personality disorder

Further investigation

Is there anything else you would especially like to know about this patient?

- What is CIDP and are there any implications in treating her psychiatric symptoms?
  - CIDP is chronic inflammatory demyelinating polyneuropathy, and leads to a common type of damage to nerves outside the brain and spinal cord (peripheral neuropathy)
  - It usually affects both sides of the body equally
  - The cause is an abnormal immune response against peripheral nerves
  - The specific onset triggers vary, but an initial bout of Guillane–Barré syndrome often proceeds CIDP. In many cases, the cause cannot be identified
  - CIDP is often associated with chronic hepatitis, diabetes, HIV, inflammatory bowel disease, systemic lupus erythematosus, lymphoma, and thyrotoxicosis
  - Patients often present with difficulty walking due to weakness, difficulty using arms and hands or legs and feet due to weakness, facial weakness, sensation changes (usually affects feet first, then the arms and hands), numbness or decreased sensation, pain, burning, tingling, or other abnormal sensations
  - As this is not a central nervous system (CNS) disease, depression and anxiety are not often presenting symptoms but may result secondarily due to disability and social dysfunction
  - CIDP outcomes vary
    - The disorder may continue, progressing over the long term, or may have repeated episodes of symptoms
    - Complete recovery is possible, but permanent loss of nerve function is not uncommon

Case outcome: first interim follow-up visit four weeks later

- Insists on continuing psychotherapy as a treatment of choice as she is worried about further medication use and exhibits some hypochondriacal thought processes

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  - Motivational and educational techniques are utilized to work with the patient regarding accepting medication changes that might better improve her psychiatric symptoms
  - Specifically, the serotonin-only SSRI agents are described in layman's terms, and other available antidepressants with different mechanisms of action are also described
  - Patient responds well to the analogy that some antibiotics do not clear infections so that another antibiotic with a new mechanism is tried to relieve this type of suffering
- Refuses polypharmacy but does eventually agree to switch from the SSRI monotherapy to a norepinephrine–dopamine reuptake inhibitor (NDRI) monotherapy approach with bupropion-SR (Wellbutrin-SR)
  - This new monotherapy is titrated up to 400 mg/d (200 mg twice a day) ultimately
- Calls prior to her appointment and states that she has no side effects except initial insomnia
  - For this, trazodone (Desyrel) 50 mg at bedtime is started to compensate
    - It is explained to her that it is also an antidepressant that has sedating properties that often improves sleep for patients
    - She feels comfortable with this polypharmacy as the trazodone is not being dosed fully as an antidepressant
- Overall, she has more energy and feels brighter, but still admits to social isolation, some increase in general worries, and feels more tense overall

Question

Would you increase her current medications or change strategies?

- No, the bupropion-SR is already at its highest approved dose. Waiting for clinical effectiveness is warranted
- Perhaps increase the trazodone, despite its risk of sedation, toward 400 mg /d in divided doses to obtain its maximal antidepressant effect instead of its current hypnotic-only effect
- Perhaps add a new SSRI or other serotonergic agent to treat her remaining symptoms
- Perhaps add a benzodiazepine (BZ) anxiolytic agent to treat her remaining symptoms

Case outcome: second interim follow-up visit at two months

- Given better rapport and trust, the patient agrees to start an SSRI in addition to her bupropion-SR and trazodone combination
  - Now titrated up to escitalopram (Lexapro) 10 mg/d

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- This approach allows the patient to maintain the bupropion-SR NDRI improvements (drive, motivation, energy) and wait for further effectiveness and residual symptom reduction (anxiety, agitation, avoidance)
- Adds serotonin facilitation (in addition to the existing norepineprhine/dopamine facilitation), hopefully to lower remaining anxiety and avoidant traits
- Remembering that SSRIs alone have failed to accomplish this in the past
- Patient now appreciates the need for combining antidepressants in a rational polypharmacy approach as single agents have not garnered her a remission of symptoms in many months
- Sleep improves remarkably and she is tolerating all three agents well
- She is felt to be 30% better

Attending physician's mental notes: interim follow-up visit at three months

- Despite being a little better, the patient is treatment resistant to the SSRI plus NDRI trial
- She is maximized on a combination of antidepressants that produce robust activity via serotonin reuptake inhibitor (SRI), norepinephrine reuptake inhibitor (NRI), and dopamine reuptake inhibitor (DRI) mechanisms. These transporters are all effectively inhibited now
- She has a clinically meaningful partial response but she is not a 50% responder
- As the MDD seems to be lifting, the anxiety and avoidance appear to be more problematic now to the patient
- She is side effect free, which is positive

Question

What would you do next?

- As she is a partial responder, maximizing her SSRI further makes sense
- As she is a partial responder, maximizing her serotonin antagonist reuptake inhibitor (SARI, trazodone) makes sense
- As she is a partial responder, has now failed three to four SSRIs, one NDRI and PDP, and would combine with an evidence-based augmentation agent, i.e., atypical antipsychotic, in addition to the current medications
- Consider adding a BZ anxiolytic to better treat her anxiety symptoms

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Attending physician's mental notes: second interim follow-up visit at three months

- As this patient is now more legitimately treatment resistant, continues with comorbid anxiety, personality traits, and has a history of AUD, will want to avoid controlled, or addiction-prone, medications *if possible*
- The SSRI mechanism has been maximized a fair amount over the years, yielding only partial improvements
  - Further attempts with these agents is likely futile
- Utilizing another serotonin-enhancing agent with a different mechanism of action may be helpful

Case outcome: interim follow-up visits through six months

- The patient continues the SSRI, NDRI, and SARI combination strategy as discussed previously, but agreed to be treated further with buspirone (BuSpar), which is approved for GAD and has considerable evidence for adjunctive MDD treatment
  - This drug facilitates serotonin neurotransmission further by providing 5-HT1A receptor partial agonism
  - She is titrated to 30 mg/d
- Each added medication seems to have reduced particular symptoms
  - Bupropion-SR (Wellbutrin-SR) improved energy and motivation with NDRI properties
  - Trazodone (Desyrel) improved sleep with SARI properties
  - Escitalopram (Lexapro) improved some of her generalized anxiety, worry, and restlessness with SSRI properties
  - Buspirone (BuSpar) improved her remaining GAD symptoms and depressive sadness and despondency with 5-HT1A agonism properties
- Continues to engage in avoidant, maladaptive, isolating behaviors when stressed
  - She has clear symptom reduction for many of her psychiatric disorders, but she still has psychosocial disability from her personality traits
  - From a wellness point of view, she is not in remission

Question

What would you do next?

- Escalate her current polypharmacy regimen as most agents here have some room to reach the maximum approved daily dose
- Augment with an antiepileptic such as gabapentin (Neurontin) or pregabalin (Lyrica) to treat her avoidance further
- Augment with an atypical antipsychotic to treat her avoidance further
- Augment with a BZ anxiolytic to treat her avoidance further

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- Return to psychotherapy as the treatment of choice for treating personality traits now that her other psychiatric symptoms are greatly reduced

Attending physician's mental notes: interim follow-up visits through 12 months

- Patient is doing very well and perhaps is in remission from GAD and MDD
- Still experiences depressive symptom worsening or experiences increases due to adjustment disorders that nearly tip her back into full MDEs
- Each of these situations are evaluated and processed using IPT techniques such as encouraging affect, clarification, communication analysis, and decision analysis
  - The novelty of this approach seems reasonable and salient to the patient and she makes attempts to use these techniques in her social circles
  - The patient develops some ability to monitor herself and her reactions to others, isolates herself less but still continues with her personality traits to a moderate degree, especially when stress levels are high

Case outcome: interim follow-up visits through 24 months

- The patient is side effect free
- Despite initial misgivings about polypharmacy, there has been gradual improvement and this regimen has not hurt her with any excessive side-effect burden issues, and she is accepting that each additional medication has brought further benefit
- A different psychotherapeutic approach has been helpful to a certain degree, but there is not a remission of her avoidant traits and when activated, these predispose her to depressive relapse
- Weekly IPT sessions are converted to monthly therapy booster sessions to maintain gains
- Neurologist states that the CIDP has lessened but her essential tremor is worsening perhaps due to the CIDP, secondary to her antidepressants, or due to her familial tremor history
- The patient is now alcohol sober for 12 years, and she is started on chlordiazepoxide (Librium) with reasonable reductions in her tremors

Case debrief

- Two-thirds of depressed patients have some degree of treatment-resistant depression (TRD)
- Treatment resistance in this case appeared to be low initially but was complicated by her anxiety, personality, and substance dependence comorbidities

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- This is a good example for the use of rational polypharmacy where drugs of different chemical classes and pharmacodynamic mechanisms are added sequentially to combat specific psychiatric symptoms
- This is a good example of how to use rational sequential psychotherapy
  - Each new medication added sequentially appeared to specifically improve certain subsets of MDD and GAD symptomatology and were well documented for every step in the medical record
- In this case, she was maximized on supportive-eclectic psychotherapy, then PDP, then IPT, with modest results. This may be akin to switching aggressively among antidepressant monotherapies
- This is also a good, albeit unfortunate, example of a patient who obtains very good symptom reduction, but does not achieve wellness with regards to gainful employment and interpersonal interactions
- Interestingly, another provider added a BZ anxiolytic to be used as an anti-tremor agent
  - After many years of alcohol sobriety, adding a gamma-aminobutyric acid (GABA)ergic BZ might be considered risky for addiction as alcohol utilizes the same mechanism of action
  - A 10 mg daily dose of escitalopram (Lexapro) and 30 mg of buspirone (BuSpar) daily actually lowered this patient's avoidant traits and helped allow her to move apartments to a better place, reconnect with estranged family members, and seek out people when stressed instead of avoiding them
- Shortly after this, the patient took in a stray one-eyed dog that required a prescription and a letter written to her housing board regarding its therapeutic value
  - Pet therapy might be considered yet another rational sequential psychotherapy endeavor
  - With this intervention, the patient achieved full sustained remission of her symptoms and has not had a recurrence of her psychiatric symptoms in many years
- She did not relapse into drinking or ever misuse the BZ over the next several years

Take-home points

- Many patients do not remit with SSRI treatment
- Switching monotherapies is a reasonable option, but as treatment resistance increases, then rational polypharmacy may be warranted to treat individual residual symptoms
  - CBT is likely the most extensively studied psychotherapy in the treatment of MDD and GAD, but other techniques such as PDP and IPT may also be effective