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The Case: The sleepy woman with anxiety

The Question: How can you be anxious and narcoleptic at the same time?

The Dilemma: Finding an effective regimen for recurrent, treatment resistant anxious depression while juggling complex treatments for sleep disorders

Pretest Self Assessment Question (answer at the end of the case)

Which of the following are approved treatments for treatment resistant depression?

A. Deep brain stimulation
B. Transcranial magnetic stimulation
C. Vagal nerve stimulation
D. Aripiprazole (Abilify)
E. Quetiapine (Seroquel)
F. MAO inhibitors

Patient Intake

- 44-year-old woman with a chief complaint of anxiety

Psychiatric History

- The patient had onset of anxiety and depression at about age 15, which she began self-medicating with alcohol
- After graduating from high school, she began college and was about to leave for study abroad when she experienced a panic attack for which she was treated in the emergency room
- She was then hospitalized and treated for alcohol abuse at age 18, and has remained sober ever since, although she does admit to some possible alprazolam (Xanax) abuse in 1999 as well as one overdose with alprazolam
- Her history also includes multiple hospitalizations for major depression
  - Age 19 (approximately one year after her release from the hospital for alcohol abuse) because she became suicidal
  - Age 24 due to recurrence of depression
  - Age 26 with an overdose following a divorce and recurrence of depression
  - Age 27 due to recurrence of depression
  - Age 29 after two miscarriages, with a possible postpartum element and some discontinuation of her medications at that time to try to get pregnant
  - Age 30 when she received electroconvulsive therapy (ECT): 7 sessions as an inpatient and 23 as an outpatient

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- Details of medication history unclear from available information and from patient's memory, but has received numerous psychotropic drugs including antidepressants, antipsychotics, and mood stabilizers, all with poor results
- She was much better for several years following her ECT treatment, but had severe memory impairment
- She had a recurrence of her depression one year ago severe enough to become totally disabled, necessitating resignation from a job as an office worker that she had enjoyed
- She continues to be disabled from depression and has a great deal of anxiety, subjectively more disturbed by her anxiety than by her depression

Social and Personal History

- Married since 1996 (second marriage); no children from either marriage
- Non smoker
- Husband an architect, supportive
- Little contact with her family of origin
- Few friends or outside interests

Medical History

- Narcolepsy
- Restless legs syndrome
- Nighttime urinary incontinence possibly related to highly sedating medications
- BMI 26
- BP 120/78
- Normal fasting glucose and triglycerides

Family History

- Grandmother: depression and who has received ECT with good results

Current Medications

- Bupropion (Wellbutrin XL) 450 mg/day (thinks it is helpful as she worsens if she tries to taper)
- Ziprasidone (Geodon, Zeldox) 60 mg in the morning and 180 mg at night (unsure if this is helpful)
- Lamotrigine (Lamictal) 200 mg in the morning and 150 mg at night (thinks it is helpful for her mood)

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- Gabapentin (Neurontin) 300 mg in the morning, 600 mg at noon, and 900 mg at night; occasional 100 mg as needed for breakthrough anxiety (experiences intolerable return of anxiety at much lower doses)
- Pramipexole (Mirapex) 1 mg/night for restless legs syndrome (unclear whether helpful)
- Methylphenidate extended-release (Concerta) 54 mg/day for daytime sleepiness (thinks it is helpful)
- Sodium oxybate (Xyrem) 9 mg in one dose at night for narcolepsy and daytime sleepiness (not taken in recommended split dose)
- DDAVP (the peptide Desmopressin) 0.4 mg/night for bedwetting

Based on just what you have been told so far about this patient's history and current symptoms, would you consider her to fall within the bipolar spectrum?

- Yes
- No

Would you continue her "mood stabilizing" medications?

- Yes, continue both ziprasidone (Geodon) and lamotrigine (Lamictal)
- Continue ziprasidone but discontinue lamotrigine
- Continue lamotrigine (Lamictal) but discontinue ziprasidone (Geodon)
- No, discontinue both ziprasidone (Geodon) and lamotrigine (Lamictal)

Attending Physician's Mental Notes: Initial Psychiatric Evaluation

- Nothing unexpected on mental status examination which showed depression and anxiety
- Because she has had numerous recurrences, this makes her illness appear to be somewhat unstable; however, she has not shown any overt signs of bipolarity
- The best diagnosis for this patient may be severe generalized anxiety with major depressive recurrent unipolar disorder
- Nevertheless, tactics that are useful for bipolar mood disorders may be useful in this patient
- Continuing ziprasidone (Geodon) and lamotrigine (Lamictal) may help mitigate the risk of a future relapse
- Thus, these medications were continued at the time of the initial evaluation

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Further Investigation:

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

- What about details concerning the diagnosis of narcolepsy and of restless legs syndrome, the treatments given and the responses to those treatments?
  - During the past year as her depression has recurred and worsened, she has developed excessive daytime sleepiness
  - She had an overnight sleep polysomnogram done in another city that supposedly showed sleep onset REM (rapid eye movement) periods, but you do not have a copy of the report and do not know if it was done while taking any medications, or after the withdrawal of any medications
  - During the past year she has also complained of restless legs worse in the evening when trying to fall asleep
  - Because of her diagnosis of narcolepsy, she was prescribed methyphenidate extended release (Concerta) which helps a bit for her daytime sleepiness, but because she was still sleepy, sodium oxybate (Xyrem) was added without further improvement of daytime alertness although she gets to sleep right away and also sleeps well through the night now
  - In fact, she sleeps too well through the night now, and has bed wetting, for which she has been prescribed DDAVP (Desmopressin), but it is not very helpful
  - Because of her diagnosis of restless legs syndrome, she is prescribed pramipexole (Mirapex), with equivocal results

Based on what you know so far about this patient's history, current. symptoms, and treatment responses, are you convinced her daytime sleepiness and nighttime restlessness are adequately diagnosed and treated?

- Yes
- No

Would you continue her 4 sleep disorder medications?

- Yes, continue all 4 (methylphenidate (Concerta), sodium oxybate (Xyrem), DDAVP (Desmopressin) and pramipexole (Mirapex))
- No, stop one or more of these

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Attending Physician's Mental Notes: Initial Psychiatric Evaluation, Continued

- The patient's complaint of excessive daytime sleepiness can be difficult to assess given all the medications she is taking, especially sodium oxybate (Xyrem) and gabapentin (Neurontin), which can cause excessive daytime sleepiness
- It can also be difficult to determine whether her sleepiness represents narcolepsy or really represents "hypersomnia" as an associated symptom of depression
- It can be similarly difficult to determine whether her restless legs represent restless legs syndrome or really represent psychomotor agitation as an associated symptom of anxiety or whether restless legs represent a side effect of bupropion (Wellbutrin) rather than restless legs syndrome
- It is even possible that her sleep disorder treatments are interfering with her treatments for depression and anxiety
- Thus, her sodium oxybate (Xyrem) was tapered, and then her DDAVP (Desmopressin) discontinued, and her pramipexole (Mirapex) was also tapered over the next month following her initial assessment

Case Outcome: First and Second Interim Followup Visits, Weeks 2 and 4

- The patient experienced some initial insomnia and restless sleep as sodium oxybate (Xyrem) was withdrawn, but this resolved in several days, as did her incontinence; her daytime sleepiness actually improved somewhat but she continued to have problems falling asleep some nights
- Next, her pramipexole (Mirapex) was tapered without worsening of restless legs, or of insomnia, or mood
- Finally, her daytime gabapentin (Neurontin) was tapered to half dose with improvement in daytime sleepiness, but this was only intermittently tolerated, because of re-emergence of anxiety; however, higher gabapentin (Neurontin) doses caused daytime sleepiness
- She continued to have depression; also, her anxiety continued to wax and wane day and night, with some relief by additional doses of gabapentin (Neurontin), but, unsatisfactory overall results; if anxiety and agitation occur at night, she also has insomnia

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Considering her former response and side effects with ECT treatment, would you consider using an alternative non-drug treatment method for her refractory symptoms?

- Yes, consider ECT
- Yes, consider VNS
- Yes, consider TMS
- Yes, consider DBS

Attending Physician's Mental Notes: Second Interim Followup, Week 4

- The patient's prior response to ECT suggests that it, or a similar treatment, may be beneficial
- She is hesitant to try ECT again because of the memory loss she sustained, but may benefit from another alternative treatment strategy
- Vagal nerve stimulation (VNS) (approved for treatment-resistant depression and available at the time of this evaluation)
  - VNS involves surgical implant of a stimulation device in the upper left side of the chest (intended as a permanent implant, though it can be removed)
  - The pulse generator can be programmed to deliver electrical impulses to the vagus nerve at various durations, frequencies, and currents
  - Stimulation typically lasts 30 seconds and occurs every five minutes
  - After an initial wave of enthusiasm for this treatment, use of VNS for depression has waned due to disappointing results, high costs and some complications, include the hassle of having the stimulator and electrode removed
- Transcranial magnetic stimulation (TMS) (approved for treatment-resistant depression)
  - Generally done on an outpatient basis
  - Electromagnetic coil is placed against the scalp near the forehead and turned off and on repeatedly for 30 to 50 minutes per treatment
  - Typical treatment duration is five daily treatments a week for four to six weeks
  - Insurance coverage is variable for a course of this treatment which costs several thousand dollars
  - TMS has been best studied in patients who have failed a single antidepressant, and not for more complicated cases, or in cases with prior good or bad responses to ECT, so it is difficult to predict the chances of success for this patient
- Deep brain stimulation (DBS) (in trials for treatment-resistant depression)

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  - Involves two surgical procedures, one to implant electrodes in the brain and a second to implant a neurostimulator in the chest
  - Stimulation is generally constant but can be temporarily turned off by holding a magnetic device over the area of the chest where the neurostimulator is located
  - DBS is an experimental procedure available at only a few medical centers with research protocols that may cover some or all of the costs
  - Risks and benefits of DBS remain unknown in treatment resistant depression, so DBS is reserved for patients who have failed many treatments, such as this patient
- After discussion of these options, the patient asked to defer action on them so she could research VNS, TMS and DBS, and in the meantime, she asked to try some other medications

Would you continue her methylphenidate extended release (Concerta) for daytime sleepiness?

- Yes
- No

Attending Physician's Mental Notes: Second Interim Followup, Week 4, Continued

- On one hand, methylphenidate extended release (Concerta) seems to be helpful for her daytime sleepiness and one could even consider raising the dose to try to alleviate her depression
- On the other hand, this could risk making her anxiety worse and, to the extent that daytime sleepiness is related to sedating medications' side effects, it may be better to adjust those
- For now, the patient is not willing to stop the stimulant, and after a discussion of risks and benefits, methylphenidate was continued
- Spoke with husband who is supportive and denies any marital conflict

Would you consider adding any of the following medications to her regimen?

- Lithium (to boost mood and mitigate risk of cycling)
- Monoamine oxidase inhibitor (MAOI) (to boost mood)
- Mirtazapine (Remeron) (to boost mood and possibly treat anxiety)
- Quetiapine (Seroquel) (to boost mood and possibly treat anxiety)
- Aripiprazole (Abilify) (to boost mood)
- None of these

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Attending Physician's Mental Notes: Second Interim Followup, Week 4, Continued

- Lithium
  - Could help to boost her mood and mitigate risk of future relapse
  - If added it may not be necessary to give her a full dose as she is already on other mood stabilizing medications
- MAOI
  - May help boost mood, as this has been effective for patients with anxious depression
  - However, this could also be activating for some patients and cause problems with sleep and anxiety
  - If added, an MAOI would require discontinuation of bupropion
  - Transdermal selegiline (Emsam) does not require dietary restriction and may be a preferable formulation
- Mirtazapine (Remeron)
  - May boost mood and also potentially treat anxiety
- Quetiapine (Seroquel)
  - May boost mood (approved for depressed phase of bipolar disorder and as adjunct for unipolar depression)
  - May also be helpful for anxiety (anecdotal reports as adjunct)
  - If added, it may require careful dosing to avoid daytime sedation
- Aripiprazole (Abilify)
  - May boost mood (approved as adjunct for unipolar depression)
  - Can be activating and cause problems with anxiety
- The patient was encouraged to switch from bupropion (Wellbutrin) to mirtazapine (Remeron), but instead opted for aripiprazole (Abilify) augmentation of her current medications (bupropion, lamotrigine, gabapentin, methylphenidate), while discontinuing ziprasidone.

Case Outcome: Multiple Interim Followups to Week 24

- Aripiprazole (Abilify) titration from 2 mg to 5 mg while ziprasidone (Geodon) was discontinued showed no real changes good or bad for the first month (week 12)
- Aripiprazole was then increased to 10 mg, with slight improvement (week 16)
- After a second month at 10 mg of aripiprazole, no further improvement in depression and anxiety and overall results not satisfactory (week 20)
- The patient was switched from aripiprazole to quetiapine (Seroquel), which was not associated with improvement of mood or anxiety, and made her sleepiness worse (by week 24)
- The patient was offered a trial of mirtazapine (Remeron) again, and

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due to the results with quetiapine, was not willing to take it (at week 24)
- She was offered an MAOI, but said she would rather consider VNS, TMS or another round of ECT (at week 24)
- Insurance approved VNS, and the patient became essentially asymptomatic for more than 4 years

Case Debrief

- The patient has a 25-year history of recurrent anxiety and depression that appears unipolar in nature and has been somewhat responsive to antidepressants and very responsive to ECT in the past
- Her current relapse is causing her disability and is not fully responsive to the 8 medications she was taking on initial referral (bupropion, lamotrigine, ziprasidone, gabapentin, sodium oxybate, DDAVP, methylphenidate and pramipexole)
- It seems possible that her sleep symptoms are more related to her anxious depression rather than to additional diagnoses of narcolepsy and restless legs syndrome and, in any event, her treatments for these sleep disorders did not improve her symptoms; discontinuation of several sleep medications (sodium oxybate, pramipaxole and DDAVP) if anything improved her symptoms; other clinicians may have opted to continue these medications
- Following simplification of her medication regimen from 8 medications to 5, she failed to respond to augmentation with aripiprazole or with quetiapine
- Possibly because of her prior response to ECT (and a first degree relative also responded to ECT), she was an excellent candidate for VNS

Take-Home Points

- It can be difficult to determine whether insomnia with anxiety and psychomotor agitation at night, with simultaneous excessive sleepiness during the day while having poor sleep at night in a patient taking sedating medications, are due to a sleep disorder, to an anxiety disorder, to a depressive disorder or to side effects of medications
- Simplifying medication regimen from 8 medications to 5 may help determine whether some of the symptoms are due to medications and whether all medications are necessary
- The ultimate proof that her symptoms of daytime sleepiness and night time agitation are linked to her anxiety/mood disorder rather than to sleep disorders was that these symptoms abated when her depression and anxiety abated with effective treatment by VNS

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Performance in Practice: Confessions of a Psychopharmacologist

- What could have been done better here?
  - Did it take too long to get to the VNS recommendation?
  - Should she have been pushed harder to try mirtazapine or an MAOI rather than augmentation with two additional, three total, atypical antipsychotics?
  - Did it take too long to clarify the sleep issues?
  - Should we have tried harder to get a copy of the written results of the polysomnogram?
- Possible actions for improvement in practice
  - Make sure that augmentation with atypical antipsychotics is not the only option offered, or the only option offered early, since these drugs are expensive and can have notable side effects
  - Despite less robust comparative data, agents such as mirtazapine and MAOIs, and also VNS and ECT, can be considered earlier in the treatment algorithm
  - Get husband more involved as patient is at high risk for long term depression, and he is her major support system
  - Consider psychotherapy earlier rather than after VNS and assess whether the patient is a good candidate for interpersonal or cognitive behavioral approaches

Tips and Pearls

- Treatment with pregabalin (Lyrica), approved for anxiety in Europe but not in the US, rather than gabapentin (Neurontin), not approved anywhere for anxiety, may be less sedating if more expensive
- If the patient requires an MAO inhibitor, best to stop the bupropion and the methylphenidate, but lamotrigrine and gabapentin can be continued. For heroic cases unresponsive to an MAO inhibitor, stimulants such as methylphenidate can sometimes be cautiously added to an MAO inhibitor by experts monitoring cardiovascular status who are sophisticated about weighing risks and benefits

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Two-Minute Tute: A brief lesson and psychopharmacology tutorial (tute) with relevant background material for this case

– Classification and testing for narcolepsy, hypersomnia and restless legs syndrome

– Overlap of symptoms in sleep disorders with psychiatric disorders

International Classification Of Sleep Disorders
Diagnostic Criteria Of Narcolepsy

- Patient complains of excessive sleepiness or sudden muscle weakness
- Recurrent daytime naps or lapses into sleep almost daily for at least 3 months
- Possible sleep-onset REM (rapid eye movement) periods, hypnagogic hallucinations, and sleep paralysis
- With cataplexy
  - Sudden bilateral loss of postural muscle tone in association with intense emotion
- Hypersomnia not better explained by another disorder
- Should be confirmed by PSG (polysomnogram) followed by MSLT (multiple sleep latency test, see below) which should show a mean sleep latency of 8 minutes and two more sleep-onset REM periods (SOREMPs) following normal sleep
- May be confirmed by orexin levels in the cerebrospinal fluid (CSF) <110 pg/ml or, 1/3 of mean normal control levels

Narcolepsy is estimated to occur in 0.03–0.16% of the general population, with its development mostly beginning in the teens. Narcoleptic sleep attacks usually occur for 10–20 minutes and, on awakening, the patient can be refreshed for 2–3 hours before feeling the need to sleep again. Although sleep attacks occur most often in a monotonous situation, they can also occur when a person is actively conversing or eating. Symptoms of narcolepsy may include frightening hypnogogic hallucinations and sleep paralysis, which are usually coincident with SOREMPs. Not everyone with narcolepsy will have cataplexy but it is a unique feature of this disorder. An attack normally lasts a few seconds to minutes, during which the person is conscious. Some people have only minimal muscle involvement, while others can have "full-body" attacks; however, the respiratory and ocular muscles are never involved. Excessive sleepiness is the main symptom to continue with age, and it may worsen alongside the development of periodic limb movements and obstructive sleep apnea. In addition, sleep may be disrupted and include frequent awakenings (International Classification of Sleep Disorders, revised, 2001).

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Multiple Sleep Latency Test (MSLT)

- Dark comfortable room at an ambient temperature
- Smoking, stimulants and vigorous physical activity avoided during the day, only light breakfast and lunch given
- Instructions are to
  - "Lie quietly in comfy position, keep eyes closed, try to fall asleep"
- Five nap opportunities as 2 hour intervals – initial nap opportunity 1.5–3 hours after termination of usual sleep
- Between naps patient out of bed and awake
- Sleep onset determined by time from "lights out" to first epoch of any sleep stage
- To assess occurrence of REM sleep the test continues for 15 minutes from first sleep epoch
- Session terminated if sleep does not occur after 20 minutes

The Multiple Sleep Latency Test is carried out in sleep laboratories often after a night of PSG and a week filling in a sleep diary.

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The Epworth Sleepiness Scale (ESS)

Likelihood of falling asleep or dozing off when:	Chance of Dozing:			
Sitting and reading	0	1	2	3
Watching television	0	1	2	3
Sitting inactive in a public place – theater, meeting	0	1	2	3
As a car passenger for an hour without a break	0	1	2	3
Lying down to rest in the afternoon	0	1	2	3
Sitting and talking to someone	0	1	2	3
Sitting quietly after lunch without alcohol	0	1	2	3
Stopped for a few minutes while driving a car	0	1	2	3
Total Score				

Likelihood scale – rate each from 0–3 and total score

0 – would never doze
1 – slight chance of dozing
2 – moderate chance of dozing
3 – high chance of dozing

Score over 11 indicates abnormal sleepiness

The Epworth Sleepiness Scale (ESS) is a self-rating tool to enable patients and physicians to easily investigate problems with excessive sleepiness. For the most part it can be used both for looking at a day as a whole or for various times throughout a person's wake time to chart their circadian changes. As a self-rating tool, it is of course subjective and may not correlate well with objective test measures.

For the general population the average score on the ESS may be approximately 9 where as scores over 11 indicate excessive sleepiness. Interestingly those with insomnia may have scores lower than the general population, lending further weight to the theory that insomnia is a disorder of the arousal mechanisms that, as well as keeping someone awake at night, can leave someone in a state of hyperarousal during the day.

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Cardinal diagnostic features of RLS (restless legs syndrome)

1 Urge to move limbs usually associated with paresthesias or dysesthesias

2 Symptoms start or become worse with rest

3 At least partial relief with physical activity

4 Worsening of symptoms in the evening or at night

Patients with RLS experience an urge to move their legs to rid themselves of unpleasant sensations (prickling, tingling, burning or tickling; numbness; "pins and needles'' or cramp-like sensations). This movement typically relieves the sensations, which can occur at any time but are most disruptive when one is trying to fall asleep.

Primary hypersomnia

Differential Diagnosis

- Substance-induced hypersomnia
  Drug of abuse
  Medication use
  Exposure to a toxin
- Psychiatric disorder
  Major depressive disorder
  Depressed phase of bipolar disorder
- Sleep deprivation
  Symptoms reversed with increased sleep
- Post-traumatic hypersomnia
  Head trauma
  CNS injury
- Delay- or advance-phase sleep syndrome
  Circadian rhythm is shifted

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Diagnostic measures in narcolepsy and hypersomnia

	ESS	MSLT Lat. (min)	MSLT # SOREMP	CSF Hypocretin pg/ml
Narcolepsy with Cataplexy	18	3.38	3.5	96.5
Narcolepsy without Cataplexy	19	2.75	2.5	277.3
Primary Hypersomnia	17	6	0	226.8
Hypersomnia in Psychiatric Disorders	18	7.83	0	278

(data from Bassetti et al 2003)

ESS = Epworth Sleepiness Scale
MSLT = Multiple Sleep Latency Test
Lat = latency
SOREMP = Sleep onset REM Periods
CSF = Cerebrospinal Fluid

Differential diagnosis in patients with hypersomnia disorders can be difficult, but is important in choosing the best treatment. The diagnosis of primary hypersomnia is reserved for those patients in whom no other factor can be considered causal to the symptom of sleepiness.

Overlap of symptoms in sleep and psychiatric disorders

Disorder / Symptom	Major Depressive Disorder	Attention Deficit Hyperactivity Disorder	Narcolepsy	Obstructive Sleep Apnea	Shift-Work Sleep Disorder
Mood	+++	–	–	+	–
Sleepiness	+	+	+++	+++	+++
Fatigue	++	+	++	++	++
Concentration	++	+++	++	++	++

+++ Most Common ++ Common + Average – None

Many of the symptoms seen in sleep disorders are common in psychiatric disorders and vice versa. This chart compares the frequency of different symptoms among common sleep and psychiatric disorders, which is useful in making a differential diagnosis. The degree of symptom overlap among many disorders emphasizes the need to be able to recognize and treat a patient's individual symptoms, rather than use a single treatment strategy for all symptoms of a disorder.

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Posttest Self Assessment Question: Answer

Which of the following are approved treatments for treatment resistant depression?

A. Deep brain stimulation (in trials for treatment-resistant depression but not approved)
   - Involves two surgical procedures, one to implant electrodes in the brain and a second to implant a neurostimulator in the chest
   - Stimulation is generally constant but can be temporarily turned off by holding a magnetic device over the area of the chest where the neurostimulator is located
   - This is an experimental procedure available at only a few medical centers with research protocols that may cover some or all of the costs
   - Risks and benefits remain unknown so this is reserved for patients who have failed many treatments

B. Transcranial magnetic stimulation (approved for treatment-resistant depression)
   - Generally done on an outpatient basis
   - Electromagnetic coil is placed against the scalp near the forehead and turned off and on repeatedly for 30 to 50 minutes per treatment
   - Typical treatment duration is five daily treatments a week for four to six weeks
   - Insurance coverage is variable for a course of this treatment which costs several thousand dollars
   - TMS has been best studied in patients who have failed a single antidepressant, and not necessarily indicated for more complicated cases, or for cases with multiple antidepressant failures or failure of ECT

C. Vagal nerve stimulation (approved for treatment-resistant depression)
   - Involves surgical implant of a stimulation device in the upper left side of the chest (intended as a permanent implant, though it can be removed)
   - The pulse generator can be programmed to deliver electrical impulses to the vagus nerve at various durations, frequencies, and currents
   - Stimulation typically lasts 30 seconds and occurs every five minutes
   - Studied in patients with more treatment failures than those patients studied with TMS, aripiprazole, or quetiapine
   - After an initial wave of enthusiasm for this treatment, use of VNS for depression has waned due to disappointing results, high

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costs and some complications, include the hassle of having the stimulator and electrode removed

D. Aripiprazole (Abilify)(approved for treatment resistant depression)
   - Studied in patients with major depression who did not have an adequate response to one SSRI (Serotonin Selective Reuptake inhibitor) or one SNRI (Serotonin Norepinephrine Reuptake Inhibitor) antidepressant
   - Not known how well it works in patients with failures to more antidepressant treatments

E. Quetiapine (Seroquel)(approved for treatment resistant depression)
   - Also studied in patients with major depression who did not have an adequate response to one antidepressant
   - Also not known how well it works in patients with failures to more antidepressants

F. MAO inhibitors (not approved for treatment resistant depression)
   - Although almost always used for treatment resistant depression and almost never used first line, is currently only approved for first line use and not for treatment resistant depression
   - Clinical practice and numerous anecdotes suggest that some patients who do not respond to one or more antidepressants, including ECT, may respond to MAO inhibitors, but no controlled studies. Activating for some patients and may cause problems with sleep and anxiety

Answer: B, C, D and E

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