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The Case: The man whose antidepressants stopped working

The Question: Do depressive episodes become more difficult to treat and more recurrent over time?

The Dilemma: When can you stop antidepressant treatment and what do you do if medications that worked in the past no longer work?

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

When should antidepressant maintenance become indefinite?

A. Following remission from one episode of major depression
B. Following remission from two episodes of major depression
C. If there is a particularly severe episode or one with suicidality, especially if a positive family history for depression
D. Following remission from three episodes of major depression
E. On a case by case basis

Patient Intake

- 63-year-old man with the worst depression and anxiety he has ever felt

Psychiatric History: First Episode

- Age 42, became depressed and anxious after his episode of atrial fibrillation
- Felt vulnerable and afraid of death
- After his hospitalization for atrial fibrillation, which resolved with medications, he felt depression, anxiety, "butterflies in his stomach" and felt like his whole body was "plugged into an electrical circuit"
- Began having suicidal thoughts
- This episode also coincided with the death of his mother
- Treatment with alprazolam (Xanax) and clonazepam (Klonopin): no improvement
- Sertraline (Zoloft) treatment 100 mg/day and he was much improved within 2–3 months, functioning normally at work but had sexual side effects
- Felt totally normal after 6 months and discontinued sertraline

Social and Personal History

- Married 33 years, 3 children
- Non smoker
- No drug or alcohol abuse

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Medical History

- Atrial fibrillation age 42, resolved with medication
- Hypercholesterolemia
- BP normal
- BMI normal
- Normal fasting glucose and triglycerides

Family History

- Mother: depression and alcohol abuse
- Maternal uncle: alcohol abuse
- Son: depression
- Daughters: one with mild depression, one with postpartum depression

Medications One Year Following the First Episode of Depression

- Antiarrhythmic
- Statin for cholesterol
- Antihypertensive
- Aspirin

Psychiatric History: Second Episode

- Relapsed into his second episode of major depression at age 52, 10 years after his first episode and 9 ½ years after stopping sertraline
- Symptoms same as last time
- Fear, anxiety, depression, “plugged into a circuit”
- Suicidal thoughts
- Symptoms worse in the morning
- Unable to function and wife had to drive him to work for 3 months
- Depression could have been triggered in part by his taking partial early retirement just before this episode, and feeling vulnerable again and worried about whether this meant his life was over
- For some reason, not given sertraline again at first, but paroxetine (Paxil) which showed no benefit
- Switched to sertraline 150 mg/day with supplemental clonazepam (Klonopin) prn anxiety, and symptoms resolved within 2–3 months but with recurrent sexual dysfunction, same as the first time
- Discontinued sertraline after 1 year

Psychiatric History: Third Episode

- Relapsed into a third episode of major depression at age 58, 6 years after his last episode, and 5 years after stopping sertraline the second time

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- Symptoms exactly the same again, with fear, anxiety, suicidal thoughts, unable to function, symptoms worse in the morning
- Was not started on sertraline again because of prior sexual dysfunction, but given bupropinon SR (Wellbutrin SR), but no improvement after 8 weeks
- Added sertraline again, and helped after 8 weeks (completely normal) and stopped bupropion but continued sertraline for a year and then discontinued it

Psychiatric History: Fourth Episode

- Relapsed into a fourth episode of major depression at age 61, 3 years after his last episode and 2 years after discontinuing sertraline for the 3rd time
- The patient had gone back to work, had been very successful again, and retired again
- Brought up worries about his mortality again
- However, doing volunteer work and this helps a bit
- This time, given venlafaxine XR (Effexor XR) and this worked even faster than before and he did not have sexual dysfunction, but discontinued it after less than a year

Based on just what you have been told so far about this patient's history and recurrent episodes of depression, do you think it was a mistake to allow him to discontinue his antidepressant after

- this last fourth episode?
- after his third episode?
- after his second episode?

Psychiatric History: Fifth Episode

- Patient has been suffering with fifth episode for 15 months
- New psychosocial factors from marital difficulties seem to have triggered this episode
- Same symptoms as before
- The referring psychiatrist has given venlafaxine 75–150 mg, which worked for his last (fourth) episode, but no response this time to 8 weeks of treatment at this dose, plus another 8 weeks at 375 mg/day (4 months total treatment)
- This is very atypical for him, where antidepressants worked quickly and robustly in the past
- Has severe psychomotor retardation and strong thoughts but no active plans for suicide
- For months 5 through 11, venlafaxine was augmented with
  - Dextroamphetamine (Dexedrine) 20 mg/day

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  - Buspirone (Buspar) 30 mg/day
  - Clonazepam 2 mg in the morning and 2 mg at night
  - Lorazepam (Ativan) 2 mg in the morning and 2 mg at night
- This treatment regimen associated with only a partial response, and continuing depression, anxiety, guilt, hopelessness and suicidal ideation
- Switched the venlafaxine back to sertraline 200 mg/day which had worked in the past, along with continuing the same augmentation medications above, but no response for months 12 through 15 of treatment of this fifth episode
- He seems to have developed treatment resistant depression
- Would this have happened in any event, or could this have been prevented by earlier maintenance treatment?
- He now presents to you 15 months into his fifth episode of major depression, not responding to standard treatments

Attending Physician's Mental Notes: Initial Psychiatric Evaluation

- Patient has been suffering through fifth episode of depression for 15 months
- Here is a case that indeed is linked to psychosocial stressors, but seems to have new episodes of depression coming closer and closer together following discontinuation of his antidepressant
- First recurrence 9½ years after stopping sertraline the first time
- Second recurrence 5 years after stopping sertraline the second time
- Third recurrence 2 years after stopping sertraline the third time
- He is now here only a year after stopping his venlafaxine following his fourth episode of depression
- Treatment guidelines are consistent with discontinuing antidepressants 9 to 12 months after remission from a first episode of depression, with long term maintenance after the second episode reserved perhaps for very severe cases. Clearly the third episode of major depression should be treated indefinitely with antidepressant maintenance, and no doubt, after a fourth episode, indefinite antidepressant maintenance is indicated
- One wonders if the fourth episode and the current fifth episode could have been prevented if he had been treated in maintenance after his third episode
- Now, attending physician is a bit worried that the medications will not work as well this time
- Perhaps changes have occurred in the brain, with shrinkage of the hippocampus and/or prefrontal cortex due to 4 previous and now a fifth episode of depression, and that might make the current fifth episode very difficult to treat

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- Is this the natural history of treatment resistant depression in the making?

How would you treat him?

- Increase the dose of dextroamphetamine
- Increase the dose of buspirone
- Augment with bupropion
- Augment with L-methylfolate (Deplin), or thyroid or SAMe
- Augment with an atypical antipsychotic, especially aripiprazole or quetiapine
- Refer for TMS
- Refer for ECT
- Augment with mirtazapine (Remeron)
- Switch to an MAOI

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

- Has not responded to bupropion in the past, and not clear his buspirone or amphetamine is helpful, and he does not need two different benzodiazepines
- Maybe too treatment resistant for a natural product
- He has anxiety and is quite depressed, so suggest an anxiolytic/sedating/sleep inducing antidepressant like mirtazapine, while discontinuing his dextroamphetamine, buspirone, and consolidating his two benzodiazepines into one
- Could have added an atypical antipsychotic, but because of his cardiovascular status, patient wished to try mirtazapine first
- Patient willing to do all of this but discontinue his amphetamine, although he does agree to reduce the dose
- Mirtazapine 15 mg/day added and given at night
- Lorazepam discontinued and clonazepam increased to 2.5 mg in the morning and 1 mg at night
- Buspirone discontinued
- Dextroamphetamine decreased to 10 mg/day in the morning

Attending Physician's Mental Notes: First Interim Followup, Month 18 (3 months after initial psychiatric evaluation)

- Referring psychiatrist maintained the above medication treatment, and patient finally started feeling better at month 18, which the patient attributed to sertraline
- Far from well yet
- Feels worst in the morning, his usual pattern (disorganized, lacking energy, anxious)

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- Suggested his mirtazpine dose be increased and to add quetiapine (Seroquel)
- Maintained sertraline 200 mg/day
- Increased mirtazapine to 30 mg/day at night
- Maintained dextroamphetamine 10 mg in the morning
- Maintained clonazapem 2.5 mg in the morning and 1 mg at night
- Added quetiapine, tapered up to 300 mg/day

Attending Physician's Mental Notes: 2nd Interim Followup, Month 22

- Referring psychiatrist maintained the above medication treatment, but no improvement
- Still very depressed in the morning
- Recommended starting MAOI
- Washed out of sertraline, mirtazapine, dextroamphetamine
- Continued clonazapam, quetiapine
- MAOI started in 7 days (equals 7 half lives of sertraline, mirtazapine; only 5 half life washout of these is required before starting an MAOI)
- Transdermal selegilene 6 mg/24 hours prescribed

Attending Physician's Mental Notes: 3rd Interim Followup, Month 24

- Referring psychiatrist made the changes suggested above, but discontinued quetiapine because of excessive daytime sedation and some initial worsening of psychomotor retardation
- No side effects attributable to transdermal selegilene
- 4–5 weeks after starting MAOI, began to feel better
- Now he looks, if anything, a bit hypomanic, but upon close examination, patient is somewhat exhuberant about getting well, having waited 2 years to respond from this fifth episode
- Let's hope he does not stop his antidepressant this time

Case Debrief

- The patient has a 13 year history of recurrent unipolar major depressive episodes
- His first 4 episodes were readily treated to full remission and he discontinued treatment each time several months to a year after remitting
- His subsequent episodes came in an ever escalating pattern, with less and less time between them
- By the time of his fifth episode, he had become treatment resistant, and took two years to get better
- He responded to a single action agent several times (SSRI), then a dual action agent the fourth time (SNRI) and finally, after failing SSRI and SNRI

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treatment plus multiple augmentation strategies the fifth time, required an MAOI

Take-Home Points

- Major depression can be recurrent, and recurrences can possibly indicate disease progression potentially manifested as shorter and shorter periods of wellness between subsequent episodes, with eventually poor interepisode recovery, and ultimately, treatment resistance
- This may be linked to changes in brain structure and neurotrophic factors
- Patients with 3 or more episodes of depression should be treated indefinitely with antidepressant maintenance
- Antidepressant-induced sexual dysfunction can be a powerful reason to discontinue antidepressants, despite the risks of recurrence and treatment resistance

Performance in Practice: Confessions of a Psychopharmacologist

- What could have been done better here?
  - There is no question the patient should have been treated with maintenance antidepressants after his third episode of depression, possibly preventing his fourth and fifth episodes, and possibly preventing the development of treatment resistance
  - The patient was very religious and did not believe in psychotherapy, but perhaps more efforts should have been made to get him into psychotherapy to deal with his issues about his own mortality and his reactions to psychosocial stressors
- Possible action item for improvement in practice
  - Make a concerted effort to see that patients with recurrent episodes of major depression and who need maintenance treatment are not lost to followup

Tips and Pearls

- MAO inhibitors have fallen out of favor in the United States and are not used at all in many countries
- These agents remain powerful alternatives for cases like this one, with treatment resistance
- Some myths about dangers, side effects, diet and drug interactions regarding MAOIs can be dispelled with re-study of the facts about these agents, such as those shown below

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Two-Minute Tute: A brief lesson and psychopharmacology tutorial (tute) with relevant background material for this case
– How MAOIs work
– Tips on how to use MAOIs
– Brain changes in recurrent depression
– See also Case 10, Two Minute Tute, p 113

Table 1: Currently approved MAO inhibitors

Name (trade name)	Inhibition of MAO- A	Inhibition of MAO-B	Amphetamine properties
phenelzine (Nardil)	+	+	
tranylcypromine (Parnate)	+	+	+
isocarboxazid (Marplan)	+	+	
amphetamines (at high doses)	+	+	+
selegiline transdermal system (Emsam)			
brain	+	+	+
gut	+/-	+	+
selegiline low dose oral (Deprenyl, Eldepryl)	-	+	+
rasaligine (Agilect/Azilect)	-	+	-
moclobemide (Aurorix, Manerix)	+	-	-

Table 2: MAO inhibitors with amphetamine actions or amphetamines with MAO inhibitions

Drug	Comment
amphetamine	MAOI at high doses
tranylcypromine (Parnate)	also called phenylcyclopropylamine, structurally related to amphetamine
Selegiline	metabolized to L-methamphetamine
	metabolized to L-amphetamine
	less amphetamine formed transdermally

Table 3: MAO enzymes

	MAO-A	MAO-B
Substrates	5-HT	Phenylethylamine
	NE	DA
	DA	Tyramine
	Tyramine	
Tissue distribution	Brain, gut, liver, placenta, skin	Brain, platelets, lymphocytes

Table 4: Suggested tyramine dietary modifications for MAO inhibitors*

Food to avoid	Food allowed
Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish	Fresh or processed meat, poultry, and fish
Broad bean pods	All other vegetables
Aged cheeses	Processed and cottage cheese, ricotta
cheese, yogurt	
Tap and nonpasteurized beers	Canned or bottled beers and alcohol (have little tyramine)
Marmite, sauerkraut	Brewer's and baker's yeast
Soy products/tofu	

*No dietary modifications needed for low doses of transdermal selegiline or for low oral doses of selective MAO-B inhibitors.

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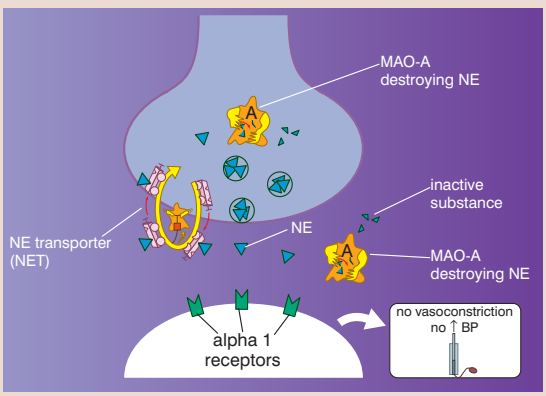

Figure 1: Normal NE Destruction

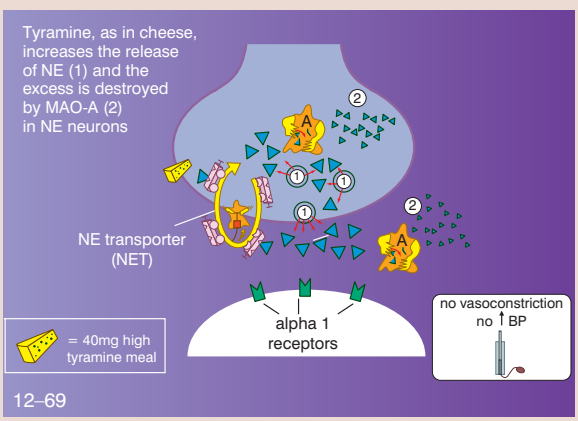

Figure 2: Tyramine increases norepinephine release

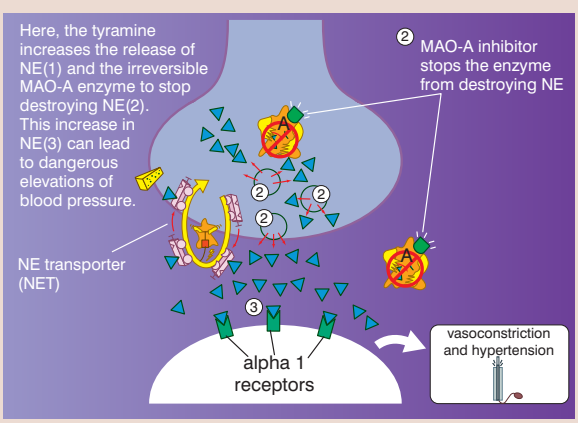

Figure 3: Inhibition of MAO-A and tyramine

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Table 5: Potentially dangerous hypertensive combos: agents when combined with MAOIs that can cause hypertension (theoretically via adrenergic stimulation)

Decongestants
phenylephrine (alpha 1 selective agonist)
ephedrine* (ma huang, ephedra) (alpha and beta agonist; central NE and DA releaser)
pseudoephedrine* (active stereoisomer of ephedrine – same mechanism as ephedrine)
phenylpropanolamine* (alpha 1 agonist; less effective central NE/DA releaser than ephedrine)
Stimulants
amphetamines
methylphenidate
Antidepressants with NRI (norepinephrine reuptake inhibition)
TCAs
NRIs
SNRIs
NDRIs
Appetite suppressants with NRI
sibutramine*
phentermine

*withdrawn from markets in the United States and some other countries

Table 6: Potentially lethal combos: agents when combined with MAOIs that can cause hyperthermia/serotonin syndrome (theoretically via SERT inhibition)

Antidepressants
SSRIs
SNRIs
TCAs (especially clomipramine)
Other TCA structures
cyclobenzaprine
carbamazepine
Appetite suppressants with SERT inhibition
sibutramine*
Opioids
dextromethorphan
meperidine
tramadol
methadone
propoxyphene

*withdrawn from markets in the United States and some other countries