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The Case: The depressed man who thought he was out of options

The Question: Are some episodes of depression untreatable?

The Dilemma: What do you do when even ECT and MAOIs do not work?

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

If a patient has low blood levels of an antidepressant at standard doses, what could this mean?

A. Pharmacokinetic failure
B. Genetic variant causing pharmacokinetic failure
C. Pharmacodynamic failure
D. Genetic variant causing pharmacodynamic failure
E. Noncompliance

Patient Intake

- 69-year-old man
- Chief complaint: unremitting, chronic depression

Psychiatric History

- Recurrent, unipolar major depressive episodes for the past 40 years, with good response to treatment and good inter-episode recovery until five years ago
- Onset then of one long, waxing and waning major depressive episode ever since
- Five years ago, relapsed on venlafaxine 225 mg after having had a good response to it
- Two years ago had nine electroconvulsive therapy (ECT) treatments with a partial response
- In the past few years since relapse on venlafaxine has tried (adequate trials, no severe side effects) essentially every known antidepressant and augmentation combination known or reported in the literature, from many capable psychiatrists and numerous consultations from local, regional, and national psychiatrists, and distinguished medical centers
  - 5 SSRIs
  - Duloxetine
  - Mitazapine
  - 2 TCAs
  - Augmentation with 5 different atypical antipsychotics
  - Augmentation with
    - Lithium
    - Thyroid
    - Buspirone

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  - L-methylfolate
  - Others
- Following ECT, given the MAOI phenelzine (Nardil) up to 105 mg/day with some orthostasis, some antidepressant response, wearing off despite increasing doses, and then all response to phenelzine wore off
- Trials even included the controversial and heroic combination of an monoamine oxidase inhibitor (MAOI) and a tricyclic antidepressant (TCA) phenelzine plus nortriptyline, all ineffective
- Came to you on phenelzine 90 mg, nortriptyline 50 mg, and occasional lorazepam, for your treatment recommendations

Medical History

- Not contributory
- Other medications:
  - Boniva for osteoporosis
  - Avapro for hypertension
  - Lipitor for hypercholesterolemia
  - Flomax for enlarged prostate
  - Melloxicam for arthritis

Social and Personal History

- Married, 3 children, 8 grandchildren
- Retired engineer
- Non smoker, no drug or alcohol abuse

Family History

- Several first degree relatives: depression
- No family history of suicide

Patient Intake

- Severely depressed and demoralized
- No joy or pleasure; sad, feeling helpless, hopeless, worthless, problems concentrating
- Past two years rates himself 9/10 in severity (10 worst)
- Wife states he is letting go and giving up

Of the following choices, what would you do?

- Add one of the new antipsychotics, asenapine, iloperidone or lurasidone that he has not taken yet
- Augment the MAOI with a stimulant, which is one of the few combinations he has not tried yet

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- Discontinue the nortriptyline and augment the MAOI
- Discontinue the MAOI and augment the nortriptyline
- Discontinue both the TCA and the MAOI and prescribe something else
- Send to another psychopharmacologist; this patient is too sick and the prognosis is poor
- Do a complete medical and endocrine and neurological evaluation to see if any underlying condition has developed that has been missed
- Look into personal and family dynamics to see if this is really a resistant depression disguising other problems
- None of the above

Further Investigation

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

- What about details concerning his medical and neurological status?
  - During the past year the patient has had extensive medical, endocrine and cancer workups, all negative
  - During the past year has also had neurological evaluation, with normal EEG, MRI
  - Neuropsychological tests consistent with severe depression but without signs of an early dementia
- What about personal and family dynamics?
  - Patient and family are indeed quite concerned about his depression, fearing he will die before he recovers
  - Patient has a long standing supportive marriage and supportive children and no major financial problems
  - Has coped with recurrent episodes of depression his whole life, bouncing back after each setback, but now has given up, frightening his family
  - No obvious reason to suspect family or personal dynamics as the source of his depression
  - However, he does have extreme negativity and a cognitive approach may be useful if he begins to get enough motivation to participate in this approach

If you would give or refer him for an experimental or "off label" protocol, test or treatment, which would you choose?

- Intravenous single injection of ketamine (NMDA N-methyl-d-aspartate antagonist) in an experimental protocol
- Send him for experimental DBS (deep brain stimulation)
- Oral riluzole (putative inhibitor of glutamate release)
- Acetylcholinesterase inhibitor in case this is really early dementia
- Send him for a quantitative EEG

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- Send him for pharmacogenomics testing
- Send him for therapeutic drug monitoring
- I would not prescribe experimental treatments off label, nor send him for an experimental protocol

Attending Physician's Mental Notes: Initial Psychiatric Evaluation

- There are very few remaining treatment options

Acetylcholinesterase inhibitor

- No evidence of dementia
- Treatment seems a long shot for his depression

TMS

- The patient may be a candidate for TMS
- However, TMS is not well documented to work in a case this severe, especially in a case with less than robust responses to ECT

DBS

- DBS is a possibility, but only a research protocol, even though it might save his life
- Only a few centers offer this procedure in the US and Canada
- Unclear how this will be paid as insurance probably does not cover
- However, some promising early results in treatment resistant depression
- Will tell patient and family and referring psychiatrist about this and provide literature but not advise action yet

Ketamine

- Intravenous single injection of ketamine is an experimental protocol
- Available as a research test at the NIMH (National Institute of Mental Health) and a few universities
- A number of studies confirm efficacy in treatment resistant major depression
- However, it only works for a few hours and then wears off and not practical to repeat it
- Not only ketamine, but several NMDA 2B subtype selective antagonists (NR2B selective antagonists) are in clinical testing, some of which are orally administered
- Too early to tell whether this will pan out and not available for open label administration, only double blind trials

Referenced EEG

- A new type of EEG protocol, referenced EEG reports promising results, but not in patients this severe and still considered a research tool
- Only available in a limited number of research centers and not proven to predict clinical response to specific antidepressants, especially in a case like this

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SPECT scans

- Some commercial clinics offer older imaging technology (SPECT is Single Photon Emission Computed Tomography) as brain scans for sale
- They do generate color pictures of brain activity that can be impressive looking to patients
- Scans are accompanied with an algorithm claiming to predict which drug to use
- Although this looks has a high-tech, scientific appearance, and raises hope, it is not well accepted in the scientific community and costs several thousand dollars not covered by insurance

Genotyping

- This approach may be useful in vulnerable populations of patients such as children or elderly and those who do not respond to many medications
- Genetic variants of cytochrome P450 (CYP45) drug metabolizing enzymes can in some cases explain unusually high or unusually low blood and brain concentrations of drugs:
  - 2D6
  - 2C19
  - 2D9
  - Others
  - This might be useful here since this patient seems not to respond to a wide number of medications now, and also has no notable side effects from them
  - Is it possible that his drug levels are low due to a drug metabolizing enzyme variant, some variant of drug absorption, or possibly noncompliance?
- Genetic variants of multiple neurotransmitter based genes, upon which many antidepressants act, may help explain both who responds to what antidepressant, and who gets side effects from what antidepressant

Phenotyping

- Determining whether a patient has high or low blood levels of a drug establishes the phenotypes of:
  - Poor metabolizers
  - Extensive metabolizers
  - Compliance/adherence
  - Pharmacokinetic variants can explain how he absorbs and metabolizes his antidepressants and thus measurement of genetic variants of CYP450 drug metabolizing enzymes may be helpful in explaining why the patient is not responding, especially if he does not generate adequate plasma and brain drug levels (pharmacokinetic)
- Advised his local treating psychiatrist to augment phenelzine with stimulant

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Attending Physician's Notes: First Interim Followup, Week 20

- Local/referring psychiatrist declined to augment MAOI with stimulant as recommended
- Decided instead to give ECT again
- Local/referring psychiatrist thought eleven ECT treatments improved him 60%
- Stopped MAOI prior to ECT and then started venlafaxine 225 mg/mirtazapine 30 mg ("California rocket fuel") as ECT began
- Post ECT, severe subjective memory problems, patient very discouraged
- Nevertheless, given maintenance ECT; venlafaxine increased to 375 mg and mirtazapine increased to 45 mg
- After ninth maintenance ECT (20th overall), developed an expressive aphasia, question of a stroke versus a complication of ECT; cardiac catheterization was normal except for a possible patent foramen ovale of unknown significance
- Consulting neurologist thought patient's aphasia was a complication of ECT
- However, referring psychiatrist thought the patient's aphasia was due to a stroke so lowered venlafaxine to 225 mg, being afraid of potential elevated BP, pulse and further cardiovascular/cerebrovascular complications
- BP remained normal and under control; aspirin added to treatment

Case Outcome: First Interim Followup, Week 20

- Phone consultation one month after the post-ECT "event" and 20 weeks since initial evaluation in the office
- Patient was still having memory problems, speech problems, and worsening depression
- Taking venlafaxine 225 mg, plus mirtazapine 45 mg, plus alprazolam prn, now augmented with aripiprazole 10 mg
- Before chasing after exotic testing and treatments considered in the mental notes during the initial psychiatric evaluation 20 weeks ago (listed above), perhaps it would be a good idea simply to send off blood for therapeutic drug monitoring to see how well he is absorbing his venlafaxine and whether there is any room for a rational and safe dose increase
- Unclear why he is no longer responding to doses of venlafaxine that have occurred would in the past, but this is frequently observed in the progression of major depressive episodes over many years
- Specifically recommended getting drug levels of venlafaxine and its active metabolite O-desmethyl-venlafaxine, and consider increasing dose of venlafaxine XR to 300 mg or 375 mg while monitoring BP and mood

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Case Outcome: Second Interim Followup, Week 24

- Phone consultation in another month showed patient's aphasia had resolved and memory improving, but mood still low; mood as bad as it was prior to ECT
- Seems more clear that aphasia was due to ECT and not to a stroke
- Venlafaxine blood levels not obtained and dose stayed at 225 mg
- Aripiprazole was increased to 15 mg
- Requested blood levels of venlafaxine/O-desmethylvenlafaxine again, and then to raise venlafaxine dose to 300 mg, as advised 4 weeks ago

Case Outcome: Third Interim Followup, Week 28

- Phone consult in another month, referring psychiatrist did get venlafaxine/O-desmethylvenlafzine blood levels, both of which were found to be low while taking a dose of 225 mg of venlafaxine XR
- Referring psychiatrist now agrees to increase venlafaxineXR to 300 mg and to discontinue aripiprazole

Case Outcome: Fourth Interim Followup, Week 32

- No improvement in depression
- Advised getting repeat venlafaxine/O-desmethylvenlafaxine blood levels again at 300 mg and then raising the dose to 375 mg if still low

Case Outcome: Fifth Interim Followup, Week 36

- Phone consultation in another month
- Venlafaxine/O-desmethylvenlafaxine levels still low at a dose of 300 mg of venlafaxine XR, so raised the dose to 375 mg
- "A pretty good few weeks" then followed but then patient relapsed a bit
- No increase of BP and no apparent side effects from venlafaxine
- Given that the blood levels of venlafaxine/O-desmethylvenlafaxine were so low on a dose of 300 mg/day, advised them to increase venlafaxine to 450 mg/day and to get another set of therapeutic drug levels

Case Outcome: Sixth Interim Followup, Week 40

- Increased venlafaxine XR dose to 450 mg/day, then got blood levels on this dose, which are only in the low normal range of the very broad therapeutic range suggested by the laboratory of venlafaxine/O-desmethylvenlafaxine
- Aphasia and memory better, mood definitely improved enough so that patient was no longer completely demoralized and was beginning to have hope
- Suggested raising the dose by 75 mg, getting levels again and if necessary, raising the dose again to 600 mg

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Case Outcome: Seventh Interim Followup, Week 52

- Dose increased to 600 mg, with full remission of depression
- However, at 600 mg dose, began to have some irritability, insomnia and 5–10 mm BP elevation, so reduced to 525 mg, and then to 450 mg of venlafaxine XR
- Tolerated it well at this dose
- BP normal by report
- Still in remission, now finally a year after the original consultation
- The case continues. . . .

Case Debrief

- A highly recurrent but readily treatable major depressive disorder suddenly turned treatment-resistant in this patient's 60s
- Not clear but hypothetically possible that this represents disease progression secondary to changes in brain functioning
- This case was looking very complicated due to nonresponse to standard and aggressive therapies at standard doses. Major depressive disorder can be treatable even in the seemingly most treatment-resistant cases
- In retrospect, this patient's transient aphasia without evidence of stroke was probably a rare complication of ECT
- Aggressive treatment does not have to be reckless but does have its risks
- It is possible for experts to augment MAOIs with a stimulant, while monitoring BP in heroic cases where the possible benefit (which has been reported with this combination) outweighs the risk (elevated BP, cardio and cerebrovascular events)
- However, this did not happen here
- Another heroic if old-fashioned option is the combination of MAOI with a TCA, well tolerated here but not effective
- Plasma drug level-guided heroic dosing of venlafaxine (or more recently desvenlafaxine) can be useful for resistant cases as it was here
- This may lead to venlafaxine dosing higher than 375 mg or desvenlafaxine dosing up to 200 mg

Take-Home Points

- Never give up
- Consider therapeutic drug monitoring before exotic research options
- Therapeutic drug levels of antidepressants such as venlafaxine are not well quantified, but if absorption is low or metabolism is high (or compliance is low), the blood levels of drug and active metabolites can still guide dosage above the normal approved therapeutic range

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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 therapeutic drug monitoring?
  - Was the second set of ECT treatments not a good idea?
- Possible action item for improvement in practice
  - Consider therapeutic drug monitoring earlier in the treatment algorithm for cases where there are inadequate therapeutic actions and low side effects
  - Consider genetic testing, especially in treatment resistant cases, the elderly and children

Tips and Pearls

- High doses of drugs taken orally sometimes deliver normal doses of drug to the brain because of various pharmacokinetic or genetic factors
- The point is how much drug is getting into the brain, not how much is taken by mouth
- The future promises better guidance of drug and dose selection by genetic tests and neuroimaging

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Two-Minute Tute: A brief lesson and psychopharmacology tutorial (tute) with relevant background material for this case
– Genotyping in depression
– Ketamine treatment of resistant depression
– Brain changes in chronic depression
– Development of treatment resistant depression

Table 1: Genotyping Neurotransmitter-Related Enzymes and Receptors in Patients with Treatment Resistant Depression?

- Still considered research tools by many
- However, beginning to be available for clinical practice applications
- Published results are not always consistently replicated
- Include variants of genes for many candidates:
  - Serotonin related receptors
    - SERT (the serotonin transporter)
    - 5HT1A receptor
    - 5HT2A receptor
    - 5HT2C receptor
  - Various glutamate receptors
  - Dopamine regulating enzymes and receptors
    - COMT (catechol-O-methyl-transferase)
    - MTHFR (methylene tetrahydrofolate reductase)
    - D2 receptor (dopamine)
  - Hypothalamic-pituitary-adrenal (HPA) axis
    - CRH1 receptor (corticotrophin releasing hormone)
    - CRH binding protein
    - Cortisol binding protein regulators (FKBP5)
  - Measuring cytochrome P450 enzyme genotypes
  - Ion channels
    - KCNK2
    - CACNA1
  - Growth factors
    - BDNF (brain derived neurotrophic factor)
    - Many others

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Table 2: Glutamate, Ketamine and the Future of Treatments for Resistant Depression

- Ketamine, like PCP/phencyclidine, is an antagonist at NMDA (N-methyl-d-aspartate) receptors
- Several groups have reported that ketamine can at least transiently improve symptoms in patients with treatment resistant depression
- Ketamine blocks NMDA receptors, and some experimental treatments target a subtype of these receptors, the NR2B receptor, hypothesizing that this is the receptor through which ketamine acts
- A novel hypothesis has been proposed for ketamine that it activates the mammalian target of rapamycin (mTOR) pathway
- This leads to increased synaptic signaling proteins
- It also increases the number and the function of new spine synapses, at least in the prefrontal cortex of rats
- These effects of ketamine are the opposite to the synaptic deficits that result from exposure to stress and thus could be the hypothetical mechanism of any therapeutic action of ketamine in treatment resistant depression, where the effects of stress upon the brain may render standard antidepressants ineffective

Table 3: Are Brain Changes Progressive in Depression?

- A frontal-limbic functional disconnection is present in depression and correlates with the duration of the current depressive episode
- Hippocampal volume loss is greater with longer periods of untreated depression
- The likelihood that a life stress precipitates a depressive episode is greatest for the first episode of depression and declines with each subsequent episode, although the risk of subsequent episodes increase as though prior episodes of depression as well as life stressors are causing subsequent episodes of depression
- More episodes of depression as well as residual symptoms both predict poorer outcome in terms of more relapses
- Antidepressants may boost trophic factors, normalize brain activity, suggesting that successful and early treatment may attenuate progressive maladaptive brain changes and improve the clinical course of the illness
- Symptomatic remission may be the clinician's benchmark for enhancing the probability of arresting disease progression
- Sustained remission may be a clinician's benchmark for reversing the underlying pathophysiology of major depression

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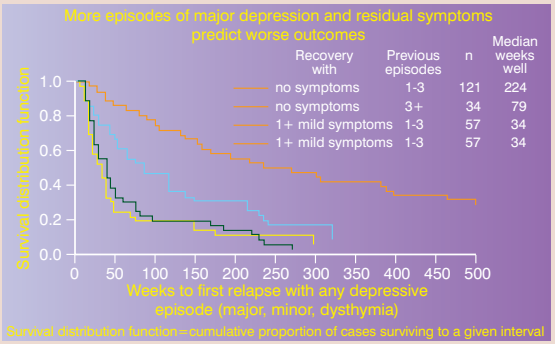

Figure 1: More Episodes of Major Depression and Residual Symptoms Predict Worse Outcomes. In other words, the depression you have, the more depression you get. Depression begets depression. Lack of remission begets relapse. This shows the importance of doing everything possible to reduce the number of episodes of depression, and also to treat every symptom to the point of remission when there is an episode of depression. The name of the game is sustained remission in the modern conceptualization of the treatment of depression.

Residual symptoms and episode count thus add to the complexity of diagnosing and treating depression and can lead to worse outcomes.

- The main finding of this study was that depressed patients who experienced recovery with no symptoms remained well for a median of 4.3 years (224 weeks) before depression recurrence, compared to approximately six months for patients who recovered with residual symptoms. Therefore, recovery with residual symptoms from depression was an important clinical marker associated with rapid episode relapse in depression
- Asymptomatic recovery included those patients with at least 80% of well interval weeks rated as the following: “Subject is returned to ‘usual self’ without any residual symptoms of the major depressive disorder, although significant symptomatology from underlying conditions may continue.”
- **Even the mildest residual symptoms, however, can negatively impact outcomes**. Patients with residual subthreshold depressive symptoms (recovery with 1+ mild symptoms)—one or more mild residual depressive symptoms—experienced on average a faster time to relapse than did asymptomatic patients.
- **Episode count, too, was a negative prognosticator**. Patients with more than three major depressive episodes (MDEs) tended to relapse earlier than those with histories of three or fewer episodes, although this did not reach significance.

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BACKGROUND

- Patients with MDD (as diagnosed using Research Diagnostic Criteria, or RDC) were followed naturalistically for 10 years or longer.
- Patients were divided on the basis of intake MDE recovery into recovery with residual subthreshold depressive symptoms (recovery with 1+ mild symptoms; N=82) and asymptomatic recovery (N=155) groups. Trained raters interviewed patients every six months for the first five years and every year thereafter.
- Depressive symptomatology was rated using the Longitudinal Interval Follow-up Evaluation (LIFE) Psychiatric Status Rating (PSR) scales.
- Recovery with 1+ mild symptoms as defined by the PSR includes those experiencing one or more depressive symptoms but of no more than a mild degree.
- P values (given according to color of lines on slide graphic): Orange vs green, P<.0001; orange vs blue, P<.0001; orange vs red, P<.0001; green vs blue, P=.013; green vs red, P=.004; blue vs red, P=.283.

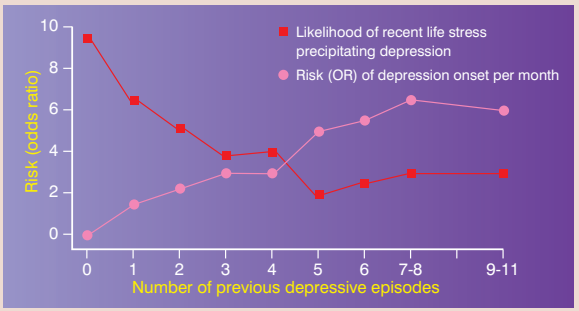

Figure 2: Progression of Depression: Adverse Effects of Each Episode on Future Episodes Which Become More Spontaneous and Less Triggered by Stress. These data are consistent with the notion that symptoms of depression and episodes of depression "kindle" subsequent episodes of depression.

- The kindling hypothesis states that previous episodes of depression change the brain, making patients more likely to experience subsequent episodes of depression
- After 4 to 5 episodes, the best predictor of subsequent episodes of depression is the number of previous depressive episodes, not stress
- Does this suggest that recurrent depression is a progressive disease?

BACKGROUND:

- Female twins from a population-based registry (N=2,395) were interviewed 4 times during a period of 9 years, forming a study

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group that contained 97,515 person-months and 1380 onsets of MDD

- To assess the interaction between life-event exposure and the number of previous episodes of MDD in predicting future MDD episodes, discrete-time survival, a proportional hazards model, and piece-wise regression analyses were used
- This pattern of results was unchanged by the addition of measures of event severity and genetic risk, as well as the restriction to "independent stressful life events"
- The same pattern of results emerged when within-person changes in the number of episodes were examined

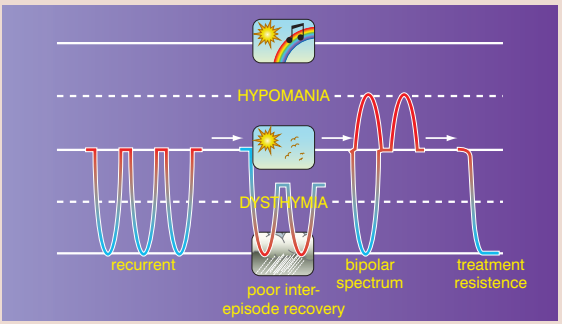

Figure 3: is Major Depressive Disorder Progressive? Studies as well as direct observations of cases over long periods of time suggest that one episode of major depression may not only increase the chances of having another, but that subsequent recurrences may not be followed by remission and only by partial treatment responses, ultimately with episodes recurring that may become treatment resistant.

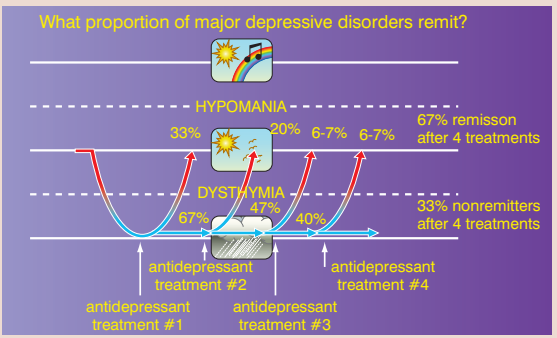

Figure 4: What proportion of major depressive disorder remit? Approximately one-third of depressed patients will remit during treatment

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with any antidepressant initially. Unfortunately, for those who fail to remit the likelihood of remission with another antidepressant monotherapy goes down with each successive trial. Thus, after a year of treatment with four sequential antidepressants taken for twelve weeks each, only two-thirds of patients will have achieved remission.

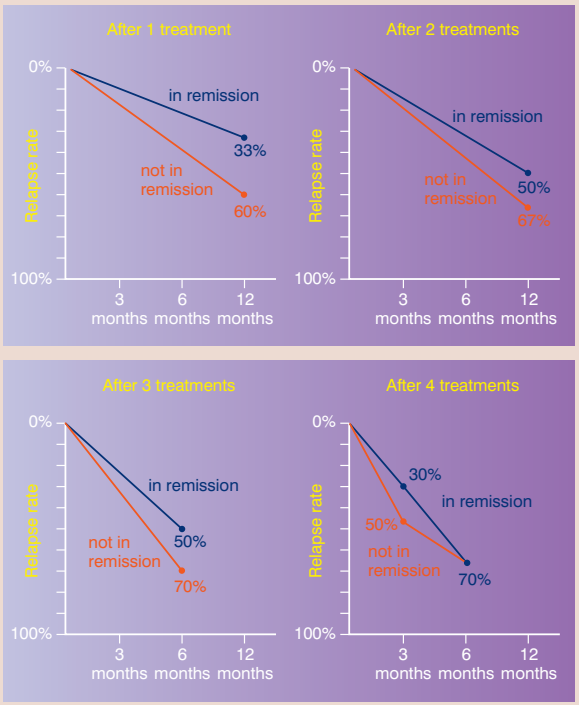

Figure 5: What Proportion of Major Depressive Disorders Relapse? The rate of relapse of major depression is significantly less for patients who achieve remission. However, there is still risk of relapse even in remitters, and the likelihood increases with the number of treatments it takes to get the patient to remit. Thus, the relapse rate for patients who do not remit ranges from 60% at twelve months after one treatment to 70% at six months after four treatments, but for those who do remit it ranges from only 33% at twelve months after one treatment all the way to 70% at six months after four treatments. In other words, the protective nature of remission virtually disappears once it takes four treatments to achieve remission.

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Posttest Self Assessment Question: Answer

If a patient has low blood levels of an antidepressant at standard doses, what could this mean?

A. Pharmacokinetic failure
   - Pharmacokinetics is the body acting upon a drug; so, if the body does not absorb or metabolize a drug in a way that normal therapeutic levels are delivered to the brain via the blood, a low blood level at standard doses can mean a pharmacokinetic failure

B. Genetic variant causing pharmacokinetic failure
   - Genetic variants of CYP450 enzymes can cause excessive metabolism of a drug and thus pharmacokinetic failure

C. Pharmacodynamic failure
   - Pharmacodynamics is the drug acting upon the body, in this case, transporters in the brain; so, if a patient has low blood levels of an antidepressant, there is not adequate opportunity to see if the drug will work, and this is not considered a pharmacodynamic failure; a pharmacodynamic failure occurs when the brain does not respond to normal levels of drug

D. Genetic variant causing pharmacodynamic failure
   - Genetic variants are considered to cause pharmacodynamic failures when despite adequate levels of drug, there is no therapeutic response

E. Noncompliance
   - low blood levels are more often caused by noncompliance/nonadherence than they are by pharmacokinetic failures

Answer: A, B and E

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