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From Resistance to Response: Evolving Strategies in MDD Management

Chapter 1

Dr. Goldberg:
Hello everyone. Welcome to our presentation today, entitled *From Resistance to Response—Evolving Strategies in Major Depressive Disorder Management*. I'm Dr. Joseph Goldberg. I'm clinical professor of psychiatry at the Icahn School of Medicine at Mount Sinai in New York. It's my pleasure to walk us through today this presentation on, well, key important aspects about treating major depressive disorder, and really focusing on treatment response and remission and the focus on residual symptoms as well.

Here is my disclosure statement.

And here are our learning objectives. So as follows, to apply measurement-based care tools to identify patients with treatment-resistant depression or patients with major depressive disorder, that's MDD, who are suboptimally managed. Second, to differentiate between depressive symptoms caused by MDD and those stemming from bipolar disorder, using evidence-based diagnostic criteria and patient history. Third, to evaluate the risks and benefits of augmentation versus switching strategies for antidepressant treatments in order to minimize adverse effects and focusing on evidence-based treatment strategies. Fourth, to develop treatment plans that specifically target the residual symptoms of depression. And finally, to critically evaluate the impact of targeting multiple pathways when treating major depressive disorder and comparing the efficacy and safety of single pathway treatments versus therapies with multiple mechanisms of action.

Chapter 2

Dr. Goldberg:
So let's begin with diagnosing suboptimally managed patients with major depressive disorder, starting with some definitions. So we use terms like response, remission, partial response. Let's operationalize those and be very concrete about that based on some consensus that comes from the literature. So in the world of major depressive disorder, or mood disorders in general, when we say someone's a responder to treatment, technically, that means that if you're measuring symptoms using some symptom-based measurement scale, you're at least 50% better than when you started out. So if you're using something like a PHQ-9 scale and you start with a 22, you're at least an 11. We'll go through some examples in just a second.

What's a partial response? That's kind of an operational definition, too. So it's not quite as robust as a response. You're less than 50% but you're more than 25%. So that's the sort of middle ground where it's not nothing, but it's also not as robust as a response. And as we'll see in just a few moments, partial responses count for something. They often inform our decisions to augment a treatment, as opposed to switch a treatment.

Now, remission is really the goal that we strive for. That means when symptoms are so low as to fall between some minimal threshold

that would be deemed of clinical significance. So may not be a zero, nothing is perfect, but if there's any symptoms left, they're thought to be not of clinically meaningful importance.

Then we sometimes use the term recovery. So that means you've achieved remission, and you've held on to it for at least 6 months. It's kind of like a sustained remission, and it also sometimes includes the notion of functional improvement as well. So some definitions will say you've reached remission; your mood is euthymic; you've held it for 6 months. And some definitions of recovery would also say: and your functioning has improved; you're working; you're socializing; you're back to your baseline there.

Then lastly, a nonresponse to treatment is when there hasn't been at least a 25% improvement from baseline.

So there's some assumptions that we make here, right? First of all, we're talking about major depressive disorder, not bipolar depression, not psychotic depression, not the negative symptoms of schizophrenia which could mimic depression, not substance-induced mood disorders. So this is, for now, MDD. We're also talking about judging response and remission in the setting of appropriate treatment. That means the right pharmacology or the right treatment with an adequate dose, adequate duration, adequate adherence to treatment. And then confounding effects, so comorbidities, intolerances that might jeopardize adherence or that might even mimic symptoms, unstable medical conditions. So all these kinds of things factor into our thinking about defining things like response, nonresponse, partial response, and so on.

Now, I said a moment or 2 ago about measurement-based care. So primary care doctors have blood pressure cuffs and thermometers and scales. We have scales too in psychiatry, but they're clinical scales, and so they're validated; they're objective measures. They're also helpful for tracking a patient compared to themself from a starting point. It's a very useful thing. So if I'm treating you for depression, and I'm using a rating scale, such as the Hamilton Rating Scale for Depression, or the Montgomery-Åsberg Depression Scale, or the Quick Inventory for Depression Symptoms, if I was in a research study, I'd have to get formal training on how to use these things and get reliability and make sure that my ratings were valid. But here, in clinical practice, as long as I'm using this scale and I'm giving it to you, I can compare you to yourself. Are you better or not better than when you started out? And what particular symptoms on a scale are improving or not improving? That's a very helpful parameter for tracking things like residual symptoms. So we'll come back to rating scales a bit more in just a moment.

Let's just go back for a moment and talk about polarity as one mode of distinction in mood disorders. So this is a Venn diagram comparing some basic features about major depressive or unipolar disorder on the left and bipolar disorder on the right. So to have bipolar disorder, you have to have had a lifetime manic or hypomanic episode. You have some statistics about prevalence and sex differences for both disorders on the side columns here. But pay attention to the middle section of the Venn diagram, these are where there's overlap. So the core symptoms of a major depressive episode are, for the most part, identical in unipolar or bipolar patients. That is to say changes in sleep, energy, concentration, appetite, self-worth, self-esteem, motor functioning, even suicidality in and of itself doesn't help differentiate. There's a little bit of research that says atypical depressive symptoms, overeating, oversleeping, maybe rejection sensitivity is a little more common in bipolar depression than unipolar depression, but it's not diagnostically specific. Psychosis can occur in depression with both unipolar and bipolar disorder, although it's a little bit more common in bipolar disorder than unipolar disorder. And DSM-5 tells us that if you have a few symptoms of hypomania that aren't enough to equal the diagnosis of a syndrome of mania or hypomania mixed features, that can actually occur in either bipolar depression or unipolar depression. So in other words, somebody with unipolar syndromal depression who talks fast, thinks fast, sleeps less without much fatigue the next day, but that's it, and it's not substantial enough to constitute an episode of hypomania, would be major depressive disorder with mixed features. And that's a new category since DSM-5 that just sort of speaks to broadening the breadth of spectrum diagnostically, more on a continuum between unipolar and bipolar disorder.

The last point to consider is the DSM-5 construct of mixed features. So you could have unipolar major depression or bipolar disorder that involves low-grade symptoms of hypomania. If it reaches syndromal criteria for a hypomanic episode, that becomes bipolar II disorder, mania is full-blown mania. What if you've only got a few symptoms that don't reach that threshold? I have unipolar depression, but I talk fast, I think fast, and I sleep less without fatigue. That may not be enough to make the definition of a hypomanic episode, but it would constitute the mixed features specifier. So DSM-5 allows us to identify an entity called major depression with mixed features, and what that turns out to be over time, we don't know yet. It's only been a construct around, really, since 2013 when DSM-5 came along. We do have some data to suggest that antidepressants may make mixed features worse, even in major depression with mixed features. But this is a construct that really allows us or invites us to speak about the continuum between unipolar and bipolar disorder, rather than hard categorical distinctions.

All right, back to rating scales, measurement-based care. Many of you may be familiar with what might be the most commonly used rating scale in depression the Patient Health Questionnaire-9, or PHQ-9. So these are 9 questions that are key to the DSM-5 criteria for a major depressive episode. It's self-administered by the patient. It can be used both to screen for the presence of a major depressive episode now, but also to track symptoms over the course of time. And it's validated, which means that if you score, well, above a 20 on this scale, that's severe depression. If you score a 5 to 9, that's mild depression. So it's a useful metric for all the reasons we just said: identifying the syndrome of major depression, quantifying its severity, and tracking course of symptoms over time.

There's other scales. Here are some others, just by way of examples, the Montgomery-Åsberg Depression Scale, the Hamilton Depression Scale. These are both clinician-rated scales, so they may not be quite as user friendly for the clinical practitioner who may be very time constrained, but they are a little more objective. They typically do require some training on the part of the one who's administrating the scale in knowing how to rate them accurately, how to differentiate what might be a side effect from a symptom of depression. Of note, this Montgomery-Åsberg Scale is very, very similar to the PHQ-9, except that asks about sadness 2 ways: subjective and objective. And other than that, it's pretty much the same core features of depression that we see in the PHQ-9.

So the pros and cons of using some of these scales I list at the bottom here. They're validated measures; they're standardized; they're commonly used in clinical trials. So if you're reading a clinical trial of a medication or even a psychotherapy and they say patients had to have a MADRS score over 25 which is, well, moderately to severe depression, you have some frame of reference for that. Also captures varied symptom domain. So some of these scales have subscales within them. The Montgomery-Åsberg scale, for instance, has an anhedonia scale built in. The Hamilton Depression Scale has some built-in anxiety measures. So these can be used for research purposes. But again, they can be a little bit time consuming. They require training. So think of these, if you're not a clinician researcher, they're things to be aware of and to know about.

Here's another dimension that's useful when we're thinking about quantifying symptoms and tracking residual symptoms. The idea of staging depression—we stage cancer, we stage all kinds of chronic illnesses. Depression can be a chronic illness. This is a scale known as the Maudsley scale, which takes into account a number of domains in addition to symptom severity. That's that second row you see there, symptom baseline severity, and you could get that from any of the scales I just showed you. But look at these other dimensions. How long has your current episode been going on? Less than a year, more than 2 years. How many treatments have you attempted in the current episode that have not been successful? Have there been augmentation treatments? Has there been ECT? As you can see, this standardized, validated scale can be rated. We have some ratings on the right, so if you come out of this with a score of 3 to 6, well, that doesn't mean nothing, but that's much milder than someone who scores an 11 to 15. If I'm seeing a patient with a major depression and the referring source says, “Joe, I'm sending you a Maudsley stage 12 depressed patient,” I have a whole different mindset, right off the bat, compared to this is somebody with a Maudsley scale of 4. And then I'm interested in, where do those points come from? Is it from number of trials in the current episode? Is it from severity? Is it from duration? So again, it's another way of quantifying and keeping track of symptoms.

Chapter 3

Dr. Goldberg:
All right, let's move on and talk about effectively managing the multifaceted complexities of major depressive disorder. By now, everybody, I think, knows the STAR*D trial from 20 years ago, which taught us that you've got about a 37% chance of remission on your first go around with an SSRI. Citalopram was used for these major depressive patients seen across a wide number of clinical settings. And we learned from STAR*D that with every successive next trial after a non-remission, the odds of remission went down, down, down, down, down to 30% at the second level of intervention, then really drops down to 13% by the third and fourth time. In other words, you might say you've got 2 good shots at this. And if, after 2 good interventions you don't get success, it doesn't mean you can't. But prognostically speaking, you need to roll up your sleeves and buckle your seat belt and anticipate that this is going to be harder to treat. Now you're getting into a higher Maudsley score. So when the patient says to you, “Well, how long till this treatment takes effect or kicks in?” or “How likely will it be that this next treatment is going to work?” by the time you're on step 3, it's not going to be as easy as it was on step 1 or step 2.

And the other thing STAR*D taught us, soberingly, is that there is no best next treatment. So by the time you head to step 2, you could switch to a different antidepressant or a cognitive therapy, or you could augment with a different antidepressant agent or a cognitive therapy. It didn't really make a world of difference. So this is not to discourage us into thinking nothing works so much as to say, don't do

the same thing over and over again. If you've gone through one or 2 iterations of, say, a monoaminergic antidepressant and you haven't had success, start thinking out of the box. You may want to think of more novel strategies or interventions, which we'll talk about as we go along, rather than just kind of reshuffling the same deck over and over again.

So speaking of antidepressants, monoaminergic antidepressants, this is a meta-analysis from just a few years ago, which shows the magnitude of effect, the likelihood of seeing a beneficial outcome or response across agents. So there's a few things to make note of here. This is called a forest plot, and those horizontal lines that you see are confidence intervals. So one thing you know from statistics is when these confidence intervals overlap, that means that the outcome is not statistically significantly different from one agent versus another. And as you look at this, you can say, hmm, these confidence intervals largely overlap. So while amitriptyline, good old amitriptyline seems to lead the pack, it's not materially different from mirtazapine or duloxetine or venlafaxine. And those drugs aren't that much different than the others, which is to say that while numerically the medicines at the top may have a somewhat better advantage, there's not a gigantic difference in the likelihood of response across these agents, which means they may differ in other ways. Their side effect profiles, certain subtypes of patients, patients with anxiety, patients with poor attentional processing, patients with sleep disorders. So the ways we think about different antidepressants shouldn't simply be just what works better than something else. It may not be as simple as that.

This is an important point, because it makes the issue of what happens after a partial response. So this is a study from some years back. It says after a 15-year follow-up, this first study of a partial response, three-quarters of patients who were partial responders, at least 25% better, but not 50% better than when they started, had residual symptoms. Usually they were somatic symptoms, fatigue, anxiety, depressed mood, sexual dysfunction, a lot had guilt or insomnia. So this is kind of a wide range of residual sorts of symptoms.

Here's another study that was done just a little bit after that. This is looking at patients who'd achieved now remission. Remission. So this is where your Hamilton Depression Score is so low as to thought to be not that clinically meaningful. Well, okay, but look, fewer than 20% were symptom free. Remission ain't perfect. And the most common residual symptoms that we're seeing even after remission, as you can see, sleep disturbance, fatigue, lack of interest. Pay attention. It's sleep disturbance. Nearly half of remitted depressed patients still have trouble sleeping. So what is that? That's a laggard symptom. You're going to diagnose a separate sleep disorder. You want to be sure that whatever treatment you're giving is not iatrogenically causing a soporific effect. But you can also anticipate when your patient is saying, "Well, I'm much less depressed, but I'm still having trouble sleeping," okay, that is one of the target symptoms that we may want to be thinking about as we try to target residual symptoms. It goes hand in hand with fatigue as well.

Here's some more data on residual symptoms. Again, this is from STAR*D, so looking at citalopram responders who didn't remit. On average, 5 residual symptom domains left over. And once again, sleep disorders high on the list, insomnia, almost 100%. Wow. Sad mood. You're less depressed, but you still have sad mood, 70% of patients. Concentration. That's looking at responders. Looking at remitters, some had problems with appetite and weight. Some had, again, sleep disturbances, especially waking up in the middle of the night, poor concentration. If you'd gotten better before week 6, that usually predicted fewer residual symptoms. But in STAR*D, a lot of patients didn't get better until after week 6, especially after the first step in starting. So harder-to-treat depressions that didn't get better with the first or second go around take longer to get better and may very well have more residual symptoms.

And one other bad thing about residual symptoms is they tend to breed more symptoms. So think of leftover symptoms can amplify. If you don't get all the cancer cells, they can come back. So while remission is the goal, and it's often elusive, part of the reason why remission is the goal isn't just because it's the right thing to do; it's because it can come back and be a predictor of relapse over the course of time.

This is another study that sort of makes that point. This is looking at patients who had residual subthreshold, or subsyndromal symptoms after being treated for a major depressive episode in the NIMH Collaborative Depression Study done many years ago, as true now as it was then. If you didn't get all the symptoms, if you didn't get into remission, if you had residual symptoms, the chances of having a full-blown relapse into another depression occurred 3 times faster than if you'd had full remission. So yet another reason why remission remains our goal.

Here's a very similar finding in bipolar disorder. Patients who had residual symptoms, once again, mimicking what we saw in the unipolar data from the Collaborative Study, much faster likelihood of seeing a full-on relapse after recovery—this is in bipolar depression—as compared to patients that really had a full, robust remission, asymptomatic.

Any residual symptoms that are most likely to predict relapse? Sleep problems. Once again, hypersomnia, weight changes, restlessness. In this particular study of all the kinds of residual symptoms that one might have, and they're all important, one might pay particular attention to residual sleep problems and appetite; weight changes and restlessness goes on your radar. This may be particularly informative in terms of anticipating the chance for relapse.

All right. So we've talked about response, partial response, remission, recovery, treatments, first steps, second steps, beyond that. Treatment-resistant definition doesn't have a universal definition. The FDA doesn't have an official definition, but clinical trials, by and large, tend to define treatment-resistant depression, or TRD, as a minimum of 2 prior treatment failures. Again, assuming adequate dose, adequate duration, and the appropriate treatment, so that you're not treating depression with the benzodiazepine or you're not treating depression with a stimulant; you're using something that has an evidence base to treat depression.

At this moment, there are 2, and only 2, pharmacologies that carry the FDA's approval for TRD. One is intranasal esketamine, where you didn't respond to at least 2 different antidepressants of adequate dose and duration. This is from the labeling of intranasal esketamine. And then the proprietary combination of olanzapine plus fluoxetine. Again, did not respond to at least 2 separate adequate trials of different antidepressants at adequate doses and durations.

Then there's 2 other interventions that carry FDA clearance. Clearance pertains to devices. Approval pertains to pharmacologies in the world of the FDA. One is transcranial magnetic stimulation. Once again, if you haven't had a response to at least a couple of adequate pharmacotherapy trials, TMS is FDA-approved for that indication. And also a surgical intervention, vagus nerve stimulation. Here, the bar is a little higher, a nonresponse to 4 or more medications or ECT, electroconvulsive therapy, or combinations thereof.

Now, there's plenty of other things that are out there that have been studied in the setting of patients who didn't get better with something or 2 somethings or 3 somethings or 4 somethings, but these would count as the four FDA-approved or cleared interventions for TRD.

Many, but not all, atypical antipsychotics carry FDA approval as add-on therapy to a monoaminergic antidepressant after an incomplete response to that antidepressant. So that's not necessarily the same thing as TRD based on the definitions I showed you just a moment ago. Here are some examples. We have the 3 dopamine partial agonists, aripiprazole, brexpiprazole, cariprazine. Then we have olanzapine uniquely when paired with fluoxetine, which does happen to be—remember from the slide before—one of the FDA-approved pharmacologies for TRD. So olanzapine, uniquely with fluoxetine. And then quetiapine, the extended release, has its indication as an augmentation to a monoaminergic antidepressant in treatment-resistant depression.

Down here at the bottom, I had a little bit more information, so there's data, but not FDA approval for a few other interventions in treatment-resistant depression: asenapine, risperidone, iloperidone, lurasidone, ziprasidone all have data but not FDA approval for those uses.

On the right-hand side, you also see some information I provided about bipolar depression, kind of another domain of looking at atypical antipsychotics in the world of depression. Interestingly, some of these compounds have been shown to work as adjunctive therapy in major depression, but not in bipolar depression, such as aripiprazole. Some have not been studied in bipolar depression, and a few of them have their FDA indications as monotherapy for bipolar depression, such as cariprazine, olanzapine, fluoxetine, or quetiapine. Last but not least, the drug lumateperone, which is currently FDA-approved either as a monotherapy or an adjunct to lithium or valproate for bipolar depression, is currently under review at the FDA as an augmentation treatment in major depressive disorder.

Now, a moment ago, I use the word dopamine partial agonist. What is that? Well, so there's 3 drugs that are kind of like thermometers for judging ambient dopamine tone in, well, different parts of the brain. And we're especially interested in brain regions that regulate emotional processing, like the limbic system, the reward pathway, the ventral tegmental area, the nucleus accumbens. So a dopamine D2 or D3 partial agonist is a compound that will raise dopamine where we think it's too low, like in your prefrontal cortex, if you have low motivation, poor attentional processing, and lower dopamine where we think it's too high, well, like in the limbic system or the associative striatum, if there's agitation, if there's mixed features.

So the neat and interesting thing about the 3 dopamine partial agonists is these are drugs that will behave a little more like agonists at lower doses. I kind of illustrate that in this graphic toward the left. They're a bit more agonistic on the right when they're at lower doses. Whereas on the left, where they're at higher doses, these partial agonists function more like full antagonists. So you give a highish dose of aripiprazole, that's say, more than 5 or 10 mg a day, or a highish dose of brexpiprazole. Or you give a highish dose of cariprazine,

these are drugs that will function more like D2 blockers, whereas lower doses you see more of a partial agonist or even an agonist type of effect.

The other thing to pay attention to are these dissociation constants down at the bottom. The lower, the tighter the binding affinity, which may be a good thing if you're interested in targeting these receptors. And also, D3 in particular is of interest because you have a lot of these D3 dopamine receptors in the reward circuitry in the brain. What does that mean? Well, that means that if I have a drug that's got a fairly strong binding affinity for the D3 receptor, a drug, for example, like cariprazine, I might anticipate that it could potentially have some value for drive, initiative, motivation, reward-based behavior, possibly anhedonia, based on the rationale that I might speculate about hypodopaminergic tone in the reward circuitry, where there's a lot of D3 receptors.

So anyway, these are some of the concepts that we might think about in choosing from among agents. And this is a graphic that just sort of illustrates what I was saying a moment ago about the tightness with which one sees binding affinity.

So of the at least 4 dopamine receptors that we think of, maybe 5 that we think of as having importance in the brain when it comes to mood, D1 receptors are thought to play a role in indirect modulation of glutamatergic circuitry and MDA receptors, AMPA receptors, ionotropic glutamate receptors that are thought to be one of the circuits involved, one of the neurotransmitters involved in the circuitry of depression. So drugs that have some particularly strong binding affinity at the D1 receptor might have some particular role that's relevant when we think about glutamatergic circuitry. On the left-hand side, asenapine, paliperidone, lumateperone, drugs with very loose binding at the D1 receptor, as you see right in the middle, probably not going to play as much off of that circuitry, at least on speculative grounds.

Now we talk about D2 blockade, that's the classic receptor target that we think of when it comes to psychosis. And so here, high density at the D2 receptor, low dissociation constants we think of as having a particular role in terms of antipsychotic efficacy. But again, all of these drugs that are listed have potent efficacy at the D2 receptor. So there's probably more than just D2 blockade going on as we differentiate from among drugs like cariprazine or brexpiprazole or iloperidone or clozapine. This is meant more just to illustrate the extent to which D2 is playing a role. In the case of drugs like quetiapine or clozapine, we also think serotonin 2A receptor binding plays a role, even maybe a bigger role than D2 blockades. So this is just one aspect of the mechanisms.

All right, back to major depression. Back to the pragmatic question of do I switch, or do I augment something? So here's some rules of the road. This comes out of the Canadian CANMAT guidelines. So I'm shamelessly stealing from my colleagues in CANMAT. This is a useful framework. So you might think about switching from a given drug to another drug if there's just been one failed trial. But if you've not responded to 2 or more, hmmm, you might not be as hasty to say, well, on to the next thing, especially if you've got some partial response. Remember what we showed you in STAR*D, the more you've gone through successive trials, the lower and lower the likelihood of remission is. So 3 failed trials, 4 failed trials, I don't have as much of a luxury of choosing from among agents, and so I may want to retain something if I've got anything that's worth retaining. You'll switch if there's a poor tolerability issue. Now, some adverse effects are transient. They're annoying but not dangerous. Others are more dealbreaker side effects for patients. When people have studied what kinds of side effects do patients say I'll put up with, as it turns out, some more than others. Headache, for some reason, is a very common side effect with almost everything, and it's rarely a reason why patients stop the medicine. On the other hand, weight gain, sexual side effects, bye-bye. Patients tend to not like to stick around. So one will have one's work cut out for you if you're contending with those side effects and you're trying to encourage somebody to stick with something. And that can be an issue with some of the, say, TRD drugs that are known for, say, weight gain or metabolic dysregulation, like olanzapine, fluoxetine, and that may be an instance of saying this can be really helpful, and it doesn't really have a lot of other drugs like it, but there are these side effects to put up with. So one has to make the judgment call between tolerability and efficacy. Certainly, one might augment more likely if the initial drug is well tolerated.

I think this third row is extremely important. So if you haven't gotten at least a partial improvement, pull out your PHQ-9s. If you haven't seen at least a 25% drop, that means your 20 goes to a 16 or better, not a 17, not an 18; 16 or better after 6 weeks, move on. The probability of success is pretty low. Is it zero? It's never zero, but that would be a good indicator: if you haven't seen at least a 25% improvement by 6 weeks, it's probably time to move on.

If I have seen a 25% improvement, hang on to that; you can make something out of something. You might want to augment there. You might want to build things, put some bells and whistles on it. Raise the dose, augment. You can make something out of something; you can't make something out of nothing.

Less severe symptoms, less functional impairment, you have the luxury of saying we can switch. More severe impairment, hold on to what you've got and try to add to it. And last but not least, patient preference has to count for these decision-making processes.

The American Society of Clinical Psychopharmacology recently conducted a survey of about 50 international psychopharmacology experts on various aspects of the topic known as deprescribing. That means, when do you get rid of medicine because it's outlived its usefulness? It's just not helpful; it's inappropriate for one reason or another. And this was a high consensus rating. I shared these new data with you. They were just released in May of 2025. Overwhelmingly, our task force said, if you don't see that 25% improvement from baseline or clinically meaningful improvement in at least 1 core target symptom like suicidality or insomnia or anxiety, cut bait. Move on. Useful pearl, tidbit.

Symptom domains. We kind of talked about the beginning in terms of what symptoms are residual. We can break these down by, well, domains on the left, like anxiety, fatigue, insomnia, self-esteem, etc. And we might speculate about whether certain kinds of treatments might be especially viable targets. So some of this is speculative, more than evidence based, but I invite you to entertain some of these ideas. For example, anxiety as a residual symptom might beckon the value of adjunctive buspirone or another 5HT1A partial agonist, some of the atypical antipsychotics that are 5HT1A partial agonists, cognitive behavioral therapy, maybe short-term benzodiazepines. Fatigue, you probably don't want to give an anti-histaminergic drug or something that's sedating. I give some examples of non-sedating strategies here. Insomnia as a residual symptom beckons interest in the orexin pathway. We're going to say more about that in just a bit. Suicidal ideation, ketamine intravenously off label does have some data looking at suicidal ideation and an emerging database with esketamine. Suicidal behavior, impulse control, behavioral suicide attempts, lithium has its database. Mood impulsivity, mood instability, some examples listed here. So one might just sort of think along these lines, at least in terms of formulating a rationale.

So when do you switch or augment? Here's some additional factors to consider. How many interventions occurred in the current episode? The more trials that were unsuccessful, as we said, the lower the likelihood of getting a response. So, well, if it's your first or second go around, you might be a little more inclined to make a switch. But after a few trials, a la STAR*D, you might want to try to hold on to whatever you can and build something.

Are there viable alternatives? Some interventions are unique. ECT, MAOIs, ketamine, lithium, got anything else like that? Nope, nope, nope, nope, nope. Those are keepers. If there's a partial effect with one of those, you may want to hang on to those and build on them, because we don't really have another look-alike for that.

Tolerability, this is always the critical balance of risks and benefits. If an adverse effect is transient, annoying but manageable, certainly not medically hazardous, we might want to encourage someone to stick with it, carry forth, continue on as best they can to try to determine if there's a response or remission that's possible. On the other hand, if a side effect is very disturbing or cumbersome or a dealbreaker for the patient, there's no point in getting into a to-do about that. So we might want to preface for patients from the get-go that everything has potential side effects and that we will do our utmost to keep a balance sheet between risks and benefits.

Are there unique target symptoms? So maybe I'm giving you lithium to target suicidal behavior. Maybe you have concomitant neuropathic pain for which a noradrenergic agent like duloxetine, or any other SNRI for that matter, might be having some unique value. I might want to keep that in the picture because it's doing something as opposed to doing nothing. Suppose you have comorbid ADHD, and so I'm using a psychostimulant in part to target your ADHD and hoping that might help with your mood as well. That's a reasonable reason to retain a stimulant. So if there's anxiety in the picture, I might want to retain something that I believe has anxiolytic properties. Some atypical antipsychotics have anxiolytic properties. As long as I can justify a rationale to keep a medicine in the picture, it's reasonable to keep it in the picture. If I can't really justify why it's there, what it's doing, it does get harder.

And lastly, the timing of when to make a change. So you might not want to make a switch or stop something in the midst of a crisis or very severe symptoms or an emergency. You might want to augment and then pull back, as opposed to making an outright switch. Or if there's an elective switch coming up, I'm concerned about a side effect, I might want to make sure that things are psychosocially stable enough to make a switch, timing it reasonably properly.

Other factors to consider. So trial length. I think I had mentioned earlier that you'd like to see at least an inkling of improvement by 2 weeks, but an adequate trial may be longer in either chronic depression, anxious depression, or more treatment-resistant depression, so you don't want to prematurely switch if an adequate trial hasn't occurred. Plus adequate dosing. So have you been on an adequate

dose? 25 mg of sertraline is not an adequate dose. Venlafaxine, you want to get to at least 150 mg to invoke the SNRI properties. So just to be mindful of that.

Pharmacogenetics sometimes can be helpful. If I'm giving someone a medication that is a substrate for a cytochrome P450 enzyme, and they happen to be either an ultra-rapid metabolizer or a poor metabolizer of that enzyme, they'll have trouble with that drug, because they're either going to break it down too fast if they're an ultra-rapid metabolizer, or if they're a poor metabolizer at that enzyme, and the drug I'm giving them is a pro-drug that has to convert to an active metabolite, they're not going to break it down. So venlafaxine has to be converted by 2D6 to make desvenlafaxine to be biologically active. If I'm a 2D6 poor metabolizer, my venlafaxine is going nowhere. It's going to build up and I'll just get side effects. So that's sometimes a helpful consideration when thinking should I switch drugs to a substrate that goes through a different metabolic pathway?

Adherence. Never assume. Always ask. Never assume. And lastly, comorbidities, it would be a shame to conclude, gee, this drug didn't work, but I failed to address your alcohol use disorder or your cannabis use disorder, or your untreated PTSD, or your untreated ADHD, or your untreated bulimia, etc. So make a comprehensive assessment of all diagnoses before making a determination about the best next step in treatment.

So now, so you're going to make a switch. Should you go from like an SSRI to an SNRI? We teach this to people. We've been taught it ourselves, or, well, you're broadening the spectrum. You're going from a 2-door to a 4-door. You're going up a model. Well, sort of. I mean, this is a meta-analysis done almost 20 years ago, and what it ended up saying was, yeah, if you go from an SSRI to an SNRI, you do get some greater degree of response, but it's not gigantic, so you might go up by like 30% better chance. Well, that's not bad, is it? Well, it's okay, but it's not leaps and bounds. So the idea of going from one class to another or broadening the spectrum is okay, but don't get too caught up with that as we go along.

Let me just amplify what I said a moment ago about anxiety at baseline. This was again from the STAR*D study, looking at major depression patients with high baseline anxiety symptoms. So not necessarily an anxiety disorder, just high anxiety symptoms. And as you can see here, it took longer to get to a response, and the number needed to treat was just higher. It took more treatment efforts to try to get a response. You had to treat more people before you're going to see a response when anxiety accompanies depression.

The other instance where longer time on drug, besides anxiety at baseline, to consider is chronic depression. So I list for you here this interesting study by Dr. Koran and colleagues looking at chronic major depression. That means that it's been there for 2 years or more. This is an old study from 25 years ago, but it makes an interesting point. It says that if you look at people who were partial responders by 12 weeks and just left them where they were, if you come back a month or 2 or more later, a sizable number will go on to actually become full remitters. So in the setting of both anxiety at baseline and chronic or persistent depression, time becomes your ally; you may not want to cut bait quite as soon. Based on what? Well, based on at least a partial response. If you've got not an inkling of a response after 6 to 8 weeks, it is probably time to move on. But if you've got a partial response, don't flinch. Time may be your ally.

I said something earlier about supratherapeutic dosing, cranking up the dose higher than, say, a manufacturer's recommended maximum. Sounds good, doesn't it? Well, you'd think. Not so much. So this was an interesting meta-analysis from a few years ago, which said, when you exceed the manufacturer's maximum therapeutic dose, when it's safe to do so, and you can't do that with a drug with a narrow therapeutic index like a tricyclic or an MAOI so much, but with SSRIs, with SNRIs, you don't get much in the way of converting a nonresponse to a response. So that column you see there, SMD, is the standardized mean difference. That's the size of the effect. That's how clinically meaningful it is to do this intervention. And, well, it's a decimal. The higher, the better. So an SMD of like 0.2 is a small effect, an SMD around 0.5 is a medium effect, and an SMD of 0.8 is a large effect. And look, we have 0.05, 0.07, 0.09. These are all pretty small effects. In other words, cranking the dose is not very likely to convert a nonresponse to a response. It might help convert a partial response to a fuller response.

Well, why not just add on bupropion? Isn't that what everybody does? And it kind of was what everybody did 25 or 30 years ago when we were very enamored of SSRIs and the emerging SNRIs. What else could you add on? Bupropion, an norepinephrine dopamine reuptake inhibitor, we think is usually pretty compatible with most SSRIs, SNRIs. If the serotonergic drug you're taking is a 2D6 substrate like fluoxetine or paroxetine or venlafaxine, bupropion will boost its level so you might get a little extra bang for the buck. Sadly, strangely, a meta-analysis of 7 trials showed—you'd think bupropion would be a dandy augmentation, but the standardized mean difference—remember, we just did that a minute ago—was pretty small. It was 0.10. So safe, and it might work, but it's not that big an effect.

And then in the STAR*D study, the citalopram nonresponders who were given adjunctive bupropion didn't fare all that well. So I don't know if this is a myth that bites the dust or how to think of it. It's certainly a safe thing to do, it's a reasonable thing to do, but in terms of anticipating outcomes, maybe not.

How about mechanisms of action? Will those inform us? I've listed here an obscene number of neurotransmitter systems on the left and their brain locations in the next column, and the serotonin receptors that are, we think, involved and their psychiatric corollaries or functions. So if I give you, say, a serotonin 1A receptor partial agonist, maybe that should help anxiety. If I give you an alpha-adrenergic drug, maybe that'll help attentional processing. If I give you an orexigenic drug, maybe that'll help with sleep-wake cycle. I mean, these are, let's say, aspirational in some ways, or at least high-level theoretically informed decisions. We're not yet at the place, though, of saying, well, we're going to give you a D1 drug to help with reward and attention. It's not quite that cut and dry yet, so I offer these up just as a way of thinking about pharmacologies when we look at what actually works.

Mechanisms don't always translate into an “aha” result. Here's an example. Vortioxetine, a novel serotonergic antidepressant, has been looked at for residual cognitive symptoms in major depressive disorder. And part of the rationale is, if you block or antagonize the serotonin 7, the 5-HT7 receptor, it is thought that that can have a pro-cognitive effect. So good idea. Let's see what happens if I give you vortioxetine alone or with an SSRI as compared to an SSRI alone. And the hypothesis, reasonable hypothesis, you ought to see some improvement in cognitive functioning on this Digit Symbol Substitution Test, and well, at least in this study, that was not the case. So, all right, does that disprove the hypothesis that maybe I'll think of vortioxetine to residual cognitive symptoms? It doesn't disprove it, just doesn't support it.

More data, more studies, other 5-HT7 antagonists? Maybe. I mean, if you're thinking like a researcher, you can ask those questions. But at this very moment, you can't say, yep, just bring in vortioxetine, it’s going to fix this.

Okay, so I said something about this serotonin 1A receptor. Here's a pretty picture that shows us these serotonin 1A receptors live in 2 places, same receptor. There's a presynaptic autoreceptor on the left; that's like the gatekeeper which spits out serotonin quanta presynaptically based on ambient tone. And there's the exact same serotonin 1A receptor on the postsynaptic dendrite of the synapse here. And it is thought that drugs that bind to the postsynaptic 1A receptor may have anxiolytic properties. That's at least the rationale for why buspirone works for anxiety. Vortioxetine has some binding there. Some atypical antipsychotics have some binding there. So there's much interest in, let's say, the neuroscience-informed approach to psychopharmacology to say, I wonder if a drug that's got some 5HT1A partial agonist effects at both pre and post, or at least postsynaptic binding, might be especially valuable for anxious depression. And lo and behold, at least some of these drugs do, like vilazodone actually has some pretty good data for anxious depression. Some of the atypical antipsychotics listed here, the partial agonist like aripiprazole, brexpiprazole, cariprazine, are not only dopamine partial agonists; they're also serotonin 1A postsynaptic partial agonists. So you can sort of play neuroscientist and think, hmm, I'm going to partially agonize this receptor that we think might play a role in anxiety. It's at least a theoretically informed rationale.

Okay, well enough theoretically informed. What else has been shown to work? This is a meta-analysis looking at augmentation strategies of traditional antidepressants when you were getting a partial response, that is to say residual symptoms. And interestingly enough, when looking at the drugs mirtazapine or mianserin—we don't have mianserin in the United States but we have mirtazapine—there was actually a pretty decent effect size. This SMD, you saw little ones for, 0.37 is right between a small and medium effect size; it’s actually pretty good. Now, you might say, well, but your mirtazapine is not an easy drug to take. It can be sedating. There might be some weight gain. True. True. Those are all things to take into the equation. But let this record show that augmentation with mirtazapine actually does have a substantial impact on treating residual symptoms after just about any monoaminergic antidepressant.

Interestingly, it could also hasten onset of response. This is a different study adding mirtazapine on to either fluoxetine or venlafaxine or bupropion. And what this slide shows, the curves on the bottom are you actually get a faster time till onset of an overall antidepressant effect using mirtazapine as a booster to any of these drugs. Do you keep it? You could. I mean, think of it as maybe a booster rocket to get things started. But if your patient is saying, “Is there any way to accelerate my response?” pull out Pierre Blier’s study from 2010 you can say, well, we could add mirtazapine. It is an evidence-based approach. It hasn't been replicated. Not the most gigantic of studies, 25 or so people per group, but it's randomized, and it is a rigorous trial. So something to think about.

How about lithium? What ever happened to lithium? It's generic. It's not just for bipolar disorder; it actually can have an augmentation value in major depressive disorder. Look at this number, 3.11 odds ratio. You are 3 times more likely to become a responder if I add

lithium on to whatever you're taking for depression than if I added on a placebo. Wow. Well, wait. Well, wait. So these are studies that were mostly done in the 1980s and '90s, which means the augmentation was largely to a tricyclic or maybe fluoxetine, which came out in late 1980s, so we don't have data with lithium in, let's call it, the more modern era. Also, lithium is not an easy drug to take. It can have its side effects. The therapeutic index is narrow; you've got to keep track of renal function. So I won't say it's fallen out of favor, but it's maybe not as thought of as high in the algorithm as it might deserve to be when you're thinking about strategies for augmentation for residual symptoms or partial response.

Chapter 4

Dr. Goldberg:
So let's take a deeper look at the symptomatology, pathophysiology, molecular drivers, and treatment for major depressive disorder.

All right. Well, let's talk about looking beyond the poly monoaminergic mechanisms that are involved in depression, starting with the glutamate system. Glutamate is the most abundant excitatory neurotransmitter in the mammalian brain. Over 40% of neurons in the mammalian brain are glutamatergic. They're excitatory. They have downstream regulatory effects over other monoamine systems. And probably the classic medication that we think about to modulate that system would be ketamine or—it's an antimere—intranasal esketamine. So the studies with those agents, by design, didn't target residual symptoms of depression. They were really looking at just treatment-resistant depression, both with IV ketamine or intranasal esketamine, with high efficacy and rapid onset. It's a novel mechanism, novel approach, but we don't really have data looking at residual symptoms per se.

Another way to get at this system is with the molecule dextromethorphan. You can boost its level up to a range that has an antidepressant effect by blocking its metabolism with the drug bupropion. That's a 2D6 inhibitor, so that raises up the level of dextromethorphan, making it an uncompetitive NMDA receptor antagonist that also has some binding affinity at what's called the sigma-1 receptor. So it's another way of trying to modulate the glutamate system. And while the studies that were done with that drug were not targeting residual symptoms of interest, in real-world practice, about 70% of prescriptions that end up getting written for dextromethorphan/bupropion tend to be as augmentation treatment to some existing SSRI or SNRI, which is to say that in real-world practice, clinicians often are using this drug as an augment or presumably for incomplete responses or residual symptoms in major depression. Sole caveat, because dextromethorphan is a substrate for 2D6, I might be cautious about using it with a 2D6 inhibitor like fluoxetine or paroxetine, just because you may get an unpredictable dose or level of dextromethorphan. But with a lot of other compounds, may be a very reasonable strategy to consider.

Another way to get at the glutamate system that I alluded to earlier is through these postsynaptic D1 receptors. Lumateperone maybe the classic example. Here is a postsynaptic D1 antagonist. So as shown in this cartoon, if you use lumateperone to inhibit or block D1 postsynaptic receptors, its way of indirectly modulating NMDA receptors and blocking them to increase more glutamate flow next door to the so called AMPA ionotropic glutamate receptor. Said differently, it's an indirect way to modulate perhaps the same end result system that we're aiming for with drugs that are direct NMDA receptor modulators like ketamine, esketamine, and probably dextromethorphan as well.

Now, we can also think about the notion of major depression with mixed features. So this is a study that's looking at lumateperone in major depression patients who have mixed features or bipolar depression patients who have mixed features. And what we see on these graphics is very comparable degrees of improvement in major depressive symptoms with lumateperone as compared to placebo, regardless of polarity, and depression symptoms come down. There's currently data under review at the FDA looking at lumateperone as an augmentation treatment to monoaminergic antidepressants and major depression.

The orexin system. I alluded to this a bit earlier. I also showed you some slides suggesting that sleep problems tend to be a common residual symptom. So we often think of dual orexin receptor antagonists like suvorexant or lemborexant. But there's also the orexin 2 receptor with unique antagonism through a novel drug called seltorexant. It's a little bit different than using a dual orexin receptor antagonist, because it's going after the orexin 2 receptor. And this drug has been looked at to target depression as a residual symptom of major depressive disorder. These are some data from one recent study suggesting that you might actually leverage the syndrome of depression, or rather the subsyndromal features of depression after an incomplete response while targeting sleep through the orexin 2 receptor. So seltorexant would be a model example of that.

All right, so we've covered a lot. Just to summarize, a majority of patients with major depressive disorder experience incomplete

remissions with standard antidepressant pharmacotherapies. It's crucial that we ensure accurate diagnoses, pick appropriate pharmacologies, assure adequate adherence, adequate trials, address comorbidities before making determinations about treatment resistance. Think about augmenting partial responses and switching strategies after you achieve—or rather fail to achieve even a partial response, augmentation if you have had at least a partial response. Please use measurement-based care. It's hard to objectify symptoms and track target symptoms over the course of time without some kind of metric. And we think about this emerging role for multimodal treatment pathways and novel transmitter systems. We've talked about beyond monoamines, the glutamatergic system, the orexin system, other pathways that might be coming along with the emerging data to move us beyond just the monoamine hypothesis of depression as one way to help try to address incomplete response and residual symptoms of major depression.

With that, I want to thank you for your attention, and we'll hope to see you again soon.