Debate and Discussion

Do Some Antidepressants Have a Faster Onset of Action Than Others?

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Pro Statement

Dr. Hirschfeld: The fundamental issue for patients and the fundamental issue with regard to faster onset is feeling better faster—without a substantial increase in side effects. I think we can get too detailed in coming up with 10 different definitions of onset of action and defining a whole number of analytical techniques, which may serve in some ways to obfuscate the concept rather than to help clarify it. The bottom line is, how quickly does the drug act in helping the patient to feel better?

We all know that very large numbers of patients would be required to detect differences in onset between medications. Most of the existing studies addressed onset of action on a post hoc basis and were not sufficiently powered to provide a definitive test. But consistent trends or patterns can tell us something useful about these drugs. When we look at various medications, some consistent trends do emerge that are suggestive of earlier onset of action for at least several of the medications.

There are differences across the various antidepressants, even though some of the drugs have very similar putative mechanisms of action. That's not hard to understand when you look at the clinical literature. There are a lot of studies showing that a patient who is unresponsive to one drug has a good chance of responding to a second drug in the same class.[1] This has occurred with several of the SSRIs (selective serotonin reuptake inhibitors). Certainly, all of us who treat patients know of many cases in which someone has not responded to one particular drug but then responded very well to another one in the same class. So I think it follows, theoretically, that even though some of these drugs are quite similar in mechanism of action, they may have different onsets of action.

It would appear that there are 3 different medications for which there is reasonable evidence of earlier onset of action: mirtazapine, venlafaxine, and citalopram.[2] This earlier onset may be explained in a number of ways. I think that some drugs can have earlier onset of efficacy, whereas others can have earlier onset of certain side effects, which may be helpful in terms of efficacy. A third group of drugs might have increased efficacy because they lack intolerable side effects.

So, although we have not been able to generate the studies with sufficient power to test adequately the whole notion of earlier onset of action, I would say that consistency

across trials, and certainly clinical experience, does indicate significant differences among various antidepressants.

Con Statement

Dr. Nierenberg: I was glad to hear the qualification of the assertion that in fact there are good data for early onset of action. And certainly, what we've heard this morning is that the design of existing trials has been inadequate to show beyond a shadow of a doubt that some of the antidepressants do work faster than others. One issue we didn't talk about enough is that the measures really are insensitive to change. Particularly with the 17-item Hamilton Rating Scale for Depression (HAM-D), the atypical symptoms are completely ignored. A lot of people can get substantially better in terms of the atypical symptoms of depression, and yet this improvement wouldn't register either on the 17-item HAM-D or on the standard Montgomery-Asberg Depression Rating Scale. This insensitivity could obscure an effect that might actually be there.

Measurements of change are also clearly too infrequent in most of the studies that have looked at time to onset. We'd have to have a fruitful debate about how frequent is frequent. How often does change have to be measured? How many measures would be needed to detect a speed of onset? It was mentioned earlier in passing, but the case mix and the subtypes of depression are generally ignored in most of the studies. We've heard about severity of illness and melancholia, but we didn't hear anything about atypical depression—a lot of outpatients are atypical. Perhaps that would also color the measurement of time to onset.

The effect of external stressors also is ignored. External stressors can change over time. At Massachusetts General, we call it *roughening.* You could at least look at persistent external stressors and see whether their presence or absence would affect time to onset.

We're all struggling with baseline assessment inflation. Bill Potter looked at this in a study that compared the direct observations of the rater with independent computer-aided telephone observations.[3] What he found was that there is not good agreement between the 2 observations—that the rater often unconsciously inflates the initial rating of severity to, let's say, bring somebody into a study. After the first or second rating, the agreement is quite good between the computer assessment and the face-to-face. So you get this pseudo-quick response: raters don't remember that they inflated ratings to get people into the trial, and when they rate them again, the scores go down very quickly. So, early change can be an artifact and has to be looked at very carefully. It might be best to have the entry criteria separate from the criteria that one uses to assess response. We have several studies in which patients only had to meet criteria to get into a study without a minimum HAM-D score. In that case, you actually decrease the effect of inflation over time.

We've talked a lot about the absence of any widely accepted definition of onset, and we need to struggle with that. There is also the absence of a predetermined delta. How much faster is clinically important? One day? Three days? A week? In order to design a study, you'd have to power it so that you knew what the predetermined delta was that would be clinically important. We could say, "If the difference in time to onset of effect is a day or two, who cares?" If it's a week, 10 days, maybe that really means something. But we at least have to predetermine a clinically important delta, and that hasn't been done for any of the studies we heard about. With the exception of the fluoxetine versus venlafaxine study, these were all post hoc, statistically significant, but we never talked about what's clinically important in terms of the actual delta.

Another problem in these studies is that dropouts are ignored. Why a patient drops out is very important. Stassen's work showed that there can be a big differential in dropouts from placebo, for example, for nonresponse versus dropouts from drug for adverse side effects.[4] At least, you'd have to model that over time to understand the whole group that you're looking at in time to response. Steve Roose talked earlier about concomitant medications being ignored and that if you had a differential in the allowed use of some benzodiazepines, for some people, you might see a faster response. In fact, a double-blind, placebo-controlled trial showed that patients treated with fluoxetine and clonazepam responded faster, in terms of reduced depressive symptoms, than patients treated with fluoxetine alone.[5] So at least you'd have to look at concomitant use of benzodiazepines—either control for it or not allow it at all.

We also talked about the placebo pattern. That's generally ignored in many of the studies that we looked at. We haven't really discussed symptomatic versus functional improvement. A study by Mark Rapaport showed, for example, in some of the minor forms of depression, that even with no difference between placebo and active drug in terms of symptomatic improvement, a broad difference in terms of functional improvement may exist.[6] So, I think we'd have to look at that amalgam, too.

So our esteemed colleagues have some interesting points. We acknowledge that faster onset might be possible, but our criticisms at least allow for a healthy skepticism. Current claims of faster onset are premature.

Pro Response

Dr. Gorman: Everything Dr. Nierenberg just said makes it that much more surprising that we have seen even hints of differences in onset among these medications. Most of these criticisms work against ever finding a difference between 2 drugs in a trial. For example, there is the issue of insufficient statistical power. Obviously, if you repeatedly find something when a study has low power, that's remarkable; it must be a very big effect. Secondly, things like measurement error and inflation of baseline scores would actually seem to improve the placebo response. Inflating the baseline score or having a general measurement

error would make it even harder to show a difference between 2 treatments. So really, what you're pointing out is that amidst a tremendous amount of technical difficulty, you still do see some suggestion of more rapid onset.

A lot of the other criticisms you had are really criticisms of depression studies in general, for example, whether our measures are sensitive to change or not. What you're saying is really not that much different from the pro side: there is a remarkable suggestion, in a very difficult field, that some medications may have an early onset of action. Given the technical difficulties, you obviously cannot say this with absolute certainty. But you do get the impression that at least 3 of these medications might distinguish themselves by having earlier onset of action than the others.

Con Response

Dr. Roose: The goal of faster onset of action is to make patients feel better faster, but we have to remember that onset of action is not the endpoint. There are treatments that can make patients feel better quickly that will never produce a satisfactory antidepressant response. For example, studies that tried to demonstrate an antidepressant effect for alprazolam demonstrated a fast onset of action for alprazolam, but the effects quickly reached a plateau and never resulted in a robust antidepressant response.[7]

We have to consider onset of action in the context of treating all phases of depressive illness. Most frequently, depression is a recurrent illness, and patients require maintenance medication. We should not value fast onset of action at the expense of tolerability or long-term effectiveness.

We also have to consider the issue of variability in patients as it affects onset of action. Studies have shown that there are early and late responders to the same medication. Patients are different, and it may not only be what medication is being taken but also who is taking the medication that will have a significant impact on onset of action.

It is an overstatement to say that there is evidence that 3 drugs work faster. If we separate efficacy from onset of action and look at differences in only the primary outcome measure in patients who respond, I do not think there are consistent data. In fact, much of the data that supposedly supports early onset comes from drug versus placebo studies, which demonstrate when medication begins to consistently separate from placebo but should not be used to make comparisons between medications.

Nonetheless, I would agree with Dr. Gorman that, despite all of the methodological difficulties, there may be a signal. But my conclusion is that this signal needs to be more rigorously investigated to see whether it is indeed a beacon rather than an illusion. However, it is premature to conclude that there is faster onset of action for any medication. We must be careful because this is not simply a scientific or a clinical issue; it is a commercial issue as well. Therefore, we have a particular responsibility to err on the side of caution.

DISCUSSION

Dr. Leon: Everyone seems to agree that the studies cited in support of early onset for specific agents have been insufficiently powered. I would add that the statistically significant differences that have been shown between drugs have been small effects. This suggests to me that a lot of tests were done, and a lot of tests were discarded, in order to show us those very small effects.

Dr. Gorman: Yes. You see a lot of cherry-picking—this business of looking for a subscore of a subscore of the HAM-D. It's highly likely that those small, highly selected differences are the result of outliers and variables like that.

I also think that dosing is a serious problem with a lot of studies we've looked at: rapid escalation to very high levels, inequalities in the doses between the active drugs.

Dr. Trivedi: One point needs to be emphasized: there are people who are fast responders. It's a phenomenon we see all the time, and understanding fast response is very important. Whether it is associated with a specific drug or not is unclear.

Another important point is that the rate of response and the number of responders are 2 different things. Efficacy and speed of onset are not the same.

Dr. Leon: That's partially true. And it's partially true because, for example, if one drug had a 100% response rate and another drug had a 10% response rate, looking only at the responders would be somewhat misleading. So you have to be a little careful about that.

Dr. Rosenbaum: Dr. Leon makes the point that it's hard to disentangle entirely the issue of having an efficacious drug from having a drug with an early onset of action. Early onset without comparable efficacy wouldn't be important. You want drugs that are at least comparable in efficacy before early onset becomes an important discriminator.

Consider stimulants. Isn't there a subgroup of people who, on the basis of the measures we use, look depressed and respond quickly and continue to respond to stimulants? That's an example of a treatment that works fast, but only in a small group of people.

Dr. Blier: I think one of the best drugs we can use to separate rapid onset and greater efficacy is lithium. In 2 double-blind studies, lithium was combined with antidepressants, and in neither of them was there a more rapid onset.[8,9] However, in these studies there was a greater efficacy at the end of the trial.

Dr. Roose: We all agree that we need to separate efficacy from onset and that onset of action is only important in drugs that are effective. However, we are still looking to define early onset of action.

Dr. Hirschfeld: What we're really looking for is the early appearance of a salient clinical benefit.

Dr. Rosenbaum: But, as you pointed out before, early clinical benefit can be a consequence of an improved side effect profile or overall greater efficacy rather than a "true"

early onset of antidepressant action. All of these are meaningful and valuable if the patient feels better. But we should define each of those things that you might be seeing early on that are different from "true" onset of action.

Dr. Roose: One way of defining meaningful onset of action is to ask what percent change in baseline HAM-D score strongly predicts eventual response. This has already been looked at by Nierenberg and colleagues.[10]

Dr. Rosenbaum: So that's a fourth category: emergence of early differences that are predictive of later response.

Dr. Culpepper: As a family physician, I would be looking for something a bit different. The HAM-D is probably not the best instrument to assess short-term change. I'd like to see data clearly showing that treatment approach A led to several behavioral differences that were measurable or visible over the first 3 weeks in a randomized trial. I'd like to see treatment continuation, hospitalization, referral or no referral, work loss, and days lost from work during the first 3 weeks of treatment as outcomes. I'd also like to see a behaviorally based functional assessment or quality-of-life scale used as a supplement to the HAM-D. Those data would convince me to change practice.

Dr. Hirschfeld: We're really talking about 2 separate things. One is being able to predict subsequent response and how early you can do that. The other is simply onset of positive clinical effect or response, which we shouldn't underestimate. It's really worth something to patients. I think when we say these 3 drugs have a quicker onset of action, we're saying that they have a quicker onset of positive clinical effects.

Dr. Roose: Can we be confident in saying that yet? Are we making an assumption that early onset is critical to compliance? What if a drug works faster but has more side effects? A lot of patients would probably tolerate a drug that takes a little longer to work, as long as it has fewer side effects.

Dr. Hirschfeld: But couldn't we let the patient decide if the trade-off is worth it?

Dr. Trivedi: We haven't explicitly addressed a question related to early onset of effect but not to total response: If a drug has an early onset—say, at 2 or 3 weeks—and response does not occur by 4 weeks, does that imply that you should stop treatment?

Dr. Roose: I think the clinician struggles most with the question of how long to continue a treatment that is not working. This is one reason that onset of action is important: it can help inform treatment decisions.

Dr. Nierenberg: We recently did some analyses based on a model proposed by Laska.[11] In this model, he turns survival on its head and says, "If you don't have the onset of response at a certain time point, what's going to be the probability of ever seeing a response?" Using this kind of analysis, we found that without a 30% reduction in symptom score at week 2, the probability that you'll never have an onset by the end of an 8 week trial is 55%. Without onset of response by week 4, the probability that you'll never have it will be 73%, and if onset does not occur by week 6, you have an 88% chance of never having it by week 8.

Dr. Stahl: The issue of early onset may boil down to 3 questions. First, is it there? We've seen some provocative hints of earlier onset for citalopram, venlafaxine, and mirtazapine, but they're just provocative.

The second question is, Why do we see hints of an earlier onset of action with these drugs? There are all sorts of methodological problems that could have exaggerated the effects, but there may also be some underlying mechanisms at work. For mirtazapine, it is probably the sedating effects, the early anxiolysis. For citalopram, it's probably the lack of early activating effects. For venlafaxine, it's a hint of this onset of ultimate efficacy.

The third question is, Is the earlier onset of action worth it? In the case of citalopram and mirtazapine, the answer is probably yes. In the case of venlafaxine, the answer is probably no, since you really have to push the dose to see the effect.

Having said all that, I still think we have to be very careful in saying that what we've seen is anything more than a suggestion of differences in onset. The data are insufficient to promote one drug as faster than another.

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