# Panel Discussion

## Chairman: Robert M. A. Hirschfeld, M.D.

**Dr. Hirschfeld:** There are a number of questions about onset of action. First, is rapid onset of action a true drug effect? Second, are there differences among the antidepressant drugs regarding the onset of action, and is a mechanism of action responsible for that?

**Dr. Charney:** I realize there is debate in the field on this issue. My own personal feeling is that to label a response, for example in the first week, as not being a drug effect is risky and is not biologically based. I think there are patients in whom their own individual biology determines if they are going to have a rapid response when they get an antidepressant and if the response is going to be due to the drugs. It is not clear to me how a priori it can be said that because the patient is getting better in a week, the effect is not due to the drug. Biology of depression is heterogeneous, and our diagnostic criteria do not define biologically homogenous groups of patients. Thus, there will be patients who, based on their biology, will respond rapidly to the antidepressant as a true drug effect.

**Dr. Thase:** It is even more important to look at the fluctuating or inconsistent levels of the response, as they may indicate whether the patient is benefiting from the placebo and other nonspecific factors or from the drug. I would also like to think that as we better understand what happens postsynaptically, we may be even better able to treat depression more quickly. There may well be newer antidepressants with different mechanisms of action, for example mirtazapine or venlafaxine, that work even more quickly than the ones we know of.

**Dr. Montgomery:** If you look at the large pooled data from placebo-controlled studies, a drug-placebo effect is emerging within the first week, indicating that all antidepressants may induce an early improvement. I would like to underline the importance of significant number of responders early in the treatment period; the available data are showing at least some evidence that some drugs like mirtazapine and venlafaxine do better in that respect than others.

**Dr. Hirschfeld:** Do data for some antidepressants suggest that higher doses are related to more rapid onset of efficacy?

**Dr. Montgomery:** Yes, evidence is clear with venlafaxine that this phenomenon is seen at a high dose and not at the lower 75-mg/day dose. Exactly what the necessary dose is, is not that clear. Venlafaxine is odd in that it seems to be a pharmacologically different drug at high doses than at low doses. But for the other drugs, I can see no advantage of raising the dose. For example, available data show that raising the initial dose of fluoxetine was associated with no extra efficacy.

**Dr. Charney:** On a theoretical basis, drugs with dual action should have a more rapid antidepressant response. The issue here is the dose, because venlafaxine at levels of approximately 225 mg/day or below is not a dual-action drug, since it is acting primarily as a serotonin reuptake inhibitor. It seems that there is no norepinephrine reuptake until doses above 225 mg/day are reached. If you can safely get the patient up to 225 mg/day or above within a week, then you may have a more rapidly acting compound. The dose-response relationships in humans are not clear for other dual-acting drugs, such as mirtazapine or milnacipran, although the animal data show effects on both norepinephrine and serotonin at low as well as high doses. It is a task in the development of new drugs and testing the drugs we have now to show the dual action in the first week of treatment.

**Dr. Thase:** Mirtazapine definitely appears to be more noradrenergic in people at 30 mg or 45 mg than it is at 10 mg or 15 mg, and both dosages cause about the same initial sedation, but the sedation lasts for a shorter time when a higher starting dose is used.

**Dr. Hirschfeld:** How do you prevent the increased placebo response rate that might occur by seeing a patient more often in order to evaluate the more rapid onset of action?

**Dr. Montgomery:** Selecting a more severely depressed population in which a placebo response is less likely is one way. You should also exclude patients who may confound the placebo issue, for example those with alcoholism, personality disorders, or recurrent brief depression. However, what might be a methodological problem in a trial design is different than what is relevant in practice. We need placebo response as clinicians, as we want to extract the best possible response from every individual patient as soon as possible.

**Dr. Hirschfeld:** Would you address the issue of combining mechanisms of action by using several different medications?

**Dr. Charney:** Let's discuss combining a selective serotonin reuptake inhibitor (SSRI) with mirtazapine first. By using the SSRI, serotonin reuptake is blocked. By adding mirtazapine, you are bringing in 2 additional antidepressant mechanisms: the $\alpha_2$ receptor antagonist effect and the 5-$HT_2$ antagonist effect. Both properties have been shown

to convey positive effects on depressed mood. To me, it makes a lot of sense to use this combination. It might be associated with a more rapid response as well as being helpful in resistant patients. However, a key issue is safety. There are few data available, but one report suggests that adding mirtazapine to SSRIs actually reduces gastrointestinal disturbances, as mirtazapine is the only antidepressant with strong and direct 5-$HT_3$ blocking properties.

**Dr. Montgomery:** I see no advantage to adding mirtazapine to tricyclics, because the tricyclics still remain dangerous. Adding it to the SSRIs undoubtedly reduces the sexual problems and nausea as well. However, whether the combination of mirtazapine with the SSRIs has faster onset of action or superior efficacy has not been properly studied yet, and it remains a very intriguing question.

**Dr. Hirschfeld:** Do data coming from various augmentation studies with pindolol suggest there are differences in terms of true illness between patients treated by psychiatrists and those treated by primary care physicians?

**Dr. Montgomery:** What is most intriguing about that data is they do indicate that in some patients there may be some neurobiological differences between first/second and third/fourth episode of depression, which may change the nature of the depression, making it less responsive to pindolol augmentation. The question about differences between primary care versus secondary care patients is difficult to answer, because in some parts of the world primary care is much more commonly used than it is elsewhere. For example, in the United Kingdom, the primary care population tends to be quite severe, as almost all depressed patients are treated in primary care.

**Dr. Rush:** We looked at the issue of chronicity of illness in a short-term comparison of 2 tricyclic antidepressants *[Rush AJ, et al. Biol Psychiatry 1994;35:711]*. We identified a group of patients that responded earlier, before 4 weeks or at 4 weeks. Another group responded later, after 4 weeks. This group tended to have more episodes of illness, poor recovery between episodes, longer length of illness, and a greater percentage of their total lifetime spent in depression of some type as compared with those who responded earlier. The other interesting detail was that the late responders did not get quite as well as the early responders. These differences appear to affect both the time to response and the degree to which patients respond.

**Dr. Thase:** It should be kept in mind that protracted depression also erodes people's psychosocial foundations and removes the coping assets that help people get better: the support of a loved one, the capacity to be confident that you can solve a problem, the hardiness with which one faces a minor adversity. So chronicity has adverse effects at simultaneous levels, one above the surface, one below.

**Dr. Hirschfeld:** Pindolol does not simply act on the 5-$HT_{1A}$ receptor; it also has β-blocking and dopaminergic properties. What is the evidence to show it is the 5-$HT_{1A}$ blocking action of pindolol that is responsible or not responsible for the changes with regard to depression?

**Dr. Charney:** First, in the clinical studies we do not have a good marker yet to demonstrate that the dose of pindolol that we are using, 7.5 mg a day, is blocking the 5-$HT_{1A}$ receptor. However, when you consider the β-blocking effect, in general β-blockers in patients who are vulnerable to depression may have some depressogenic effects. By contrast, there is no really good evidence that β-blockade will have antidepressant effect.

**Dr. Thase:** Has anyone looked to see if the blood pressure change correlates with the clinical response during pindolol treatment?

**Dr. Charney:** In our study, we measured heart rate and blood pressure *[Berman RM, et al. Am J Psychiatry 1997;154:37–43]*. Addition of pindolol did produce slight bradycardia and reduction in diastolic blood pressure, both of which are β-blocking effects. Given that our patients did not respond, there was no correlation. There is probably a different dose response for the β-blockade and 5-$HT_{1A}$ receptor blockade by pindolol. If you look at all the studies that have been conducted, there is rather convincing evidence that adding pindolol to an SSRI in first-episode depression hastens response, while this effect appears to be absent in the recurrent patients.

**Dr. Hirschfeld:** Should pindolol be added to every patient with first episode of depression starting on SSRI treatment?

**Dr. Montgomery:** In my opinion, the future of pindolol as an augmentor is not very bright, as the number of patients with first-episode depressions who actually reach mental health care professionals who think about using pindolol is going to be very small. The available evidence at the moment suggests that for first/second episode of depression, pindolol hastens the response to SSRIs. However, a substantial proportion of patients will remain nonresponders. There are very few convincing data available to show that pindolol augmentation works in treatment-refractory depressed patients. There are, however, other drugs that are showing a brighter future for treatment-resistant patients. The mirtazapine and venlafaxine data show that these drugs are working not only in first/second time depression but across the board. The lithium augmentation strategy also seems to work irrespective of number of episodes. It seems that 2 different kinds of augmentation strategy are emerging: one for treatment-resistant depression and one for first/second episode depression.

**Dr. Hirschfeld:** How long should the first episode be treated?

**Dr. Montgomery:** A couple of studies on first episodes indicate that over a 6-month period a first episode will have a higher relapse rate if you stop the treatment in the continuation period. So the first episode needs the same length of treatment, 6 months. However, in the current

state of knowledge, there are no data to support treating first-episode depression to prevent the second episode, except in severe patients with family histories. In my opinion, recurrence prevention is aimed at second episode, third episode, etc.

**Dr. Thase:** The essential goal is that patients achieve a complete recovery. If they have been able to maintain 4 to 6 months in complete recovery, then the medications should be discontinued slowly and not abruptly, even if the drug does not have a discontinuation emergence syndrome. There are changes in the brain in response to drug discontinuation that can temporarily elicit a brain response or a set of responses that look a lot like depression. So rather than expose a vulnerable person to this discontinuation effect, taper the medicine over 6 weeks to 8 weeks.

**Dr. Hirschfeld:** Dr. Thase presented very powerful data from the Frank *[Frank E, et al. Arch Gen Psychiatry 1990;47:1093–1099]* and Kupfer *[Kupfer DJ, et al. Arch Gen Psychiatry 1992;49:769–773]* studies suggesting that, in the maintenance phase, the dose of imipramine that gets patients well, keeps them well. What is the evidence whether that is equally true for the newer medications, including the SSRIs?

**Dr. Rush:** The evidence is not really there; however, my belief is, I would use unaltered dosages. We have seen some patients who do very well on 20, 30, or 40 mg of fluoxetine for 6 or 8 months, and then they appear to have some depression return. We have found that reducing the dosage helps a number of these people. In some cases, stopping the drug for a couple of weeks and then restarting it also helped, which is in essence dosage reduction of fluoxetine because of its long half-life. Although anecdotal, that evidence is something to keep in mind. I am not so sure that is true with the sertraline, paroxetine, fluvoxamine, or clomipramine.

**Dr. Thase:** The SSRIs do not have good dose-response characteristics. As a result, particularly if you have used higher doses, it is possible that you have inadvertently treated a patient at a higher dose than was therapeutically necessary. Therefore, it may be that some portion of SSRI-treated patients taking higher-than-normal doses can benefit from dose reduction. However, the dose reduction should be done with considerable caution. The patients should be seen more frequently to identify the early warning signs of deterioration of their condition. The clinicians should be vigilant to the possibility that by reducing the dose, the risk may be increased. I agree that the late-emergent dulling can be seen sometimes: patients report no joie de vivre, they are apathetic and soon feel dull. For those patients, dosage reduction very often seems helpful, and I have seen this with the other SSRIs, not just with fluoxetine.

**Dr. Montgomery:** An additional subject is the so-called SSRI "poop out" phenomenon; however, the evidence for it is very difficult to find. Clinical experience teaches us that every drug does not work in every patient or loses its efficacy in some patients. What we are discussing now is the ability of an antidepressant to reduce the chances of a new episode of depression occurring. From the excellent studies of the Pittsburgh group, it seems that imipramine would be a gold standard in that sense, as it has shown very little failure over a period of time. The only comparative study I have seen is the nefazodone versus imipramine study *[Anton SF, et al. Psychopharmacol Bull 1994;30:164–169]*, with superior and identical levels of efficacy of both compounds compared with placebo in a period of over a year. The "poop out" on imipramine in that study was because patients failed to continue because of side effects. It is not easy to discuss the "SSRI poop out" issue unless you do head-to-head comparisons. However, breakthroughs we see occurring might not be a failure of the drug but a recrudescence of illness. It may be that the nature of the depression is changing and turning into a more resistant version. I have had a number of patients that I have treated over many years for whom raising the dose on apparent failure was associated with better efficacy. I also have had a number of patients, not just with depression but with obsessive-compulsive disorder, who over the years have required higher and higher doses of drugs to get them to the level of response that allows them to function.

**Dr. Rush:** I would like to agree with that. If you think about general medical conditions in which long-term pharmacologic management is needed, such as arthritis, hypertension, cancer, or heart disease, the drug type or dose often has to be modified, usually in the upward direction. Such adjustments might be the consequence of the evolving disease biology or aging, or a combination of those factors, but the treatment has to be fine-tuned.

**Dr. Thase:** A majority of clinicians believe that "poop-out" syndrome happens, and thus, we have to be aware that people are seeing something. However, the 3 faculty members here were part of the long-term sertraline-imipramine study, and we saw no greater loss of effect over a year and a half of treatment with sertraline compared with imipramine. We cannot see "poop out" syndrome in controlled clinical studies, and therefore either it is very subtle or it does not exist.

**Dr. Rush:** Patients recruited into these studies are typically chosen not to be massively treatment resistant. By contrast, in the clinical practice we are seeing patients who have had 2 or 3 other prior drug trials combined with 20 years of illness. Even in long-term studies, we have chronically ill patients but not a lot of treatment failures. It is conceivable to think that if a patient is more chronic and a treatment-failure type, it may be more likely that situation will be similar to that seen in congestive heart failure patients, and not just with the SSRIs but with any antidepressant. The fourth episode of congestive heart failure is very difficult to treat. What we are seeing in clinical prac-

tice might be an evolution of the biology of depressive illness. This biology can start to evolve if we do not start treatment early, aggressively, and thoroughly.

**Dr. Charney:** The data presented during this symposium show that, in depressive illness, the 5-year recurrence rate is 50% to 70%. This highlights how serious and highly morbid a condition we are treating. However, there is a general feeling in the psychiatric community that polypharmacy is bad. Yet, in other medical conditions like hypertension or cancer, reaching the goal of normalizing blood pressure or cancer remission usually requires more than one medication. So given the emerging data that recurrence might convey a new or advancing negative neurobiology, I think that treatment of depression should move toward remission being the gold standard, and if that requires prescribing more than one medication, we ought to be doing it.

**Dr. Hirschfeld:** What is the optimal use of drug holidays?

**Dr. Thase:** For any reason other than occasional use to alleviate anorgasmia or other sexual dysfunction, I am absolutely against drug holidays for people with mood disorders. I am generally opposed to drug holidays even for treatment of anorgasmia, because it rewards the notion that it is good not to take your medication. It is not a problem in a patient who is adherent, who sticks with the program, and who understands that once a week or twice a month they can skip a dose so that they can have a better sex life. More frequent use of drug holidays begins to send the wrong signal to a patient.

**Dr. Rush:** I do not like drug holidays for the same reasons and would prefer to use a medicine that does not cause the problem or adjust the dosage if possible.

**Dr. Montgomery:** This symposium emphasizes the dangerous nature of depression. It is a crippling disorder with deleterious effects on social functioning and the ability to work. As such, it is targeted by the World Bank and by the World Health Organization as a disorder that should be properly treated. All the available evidence is pointing out that stopping drug treatment increases the risk of a return of that illness. If it returns, even if you reinstitute treatment quite soon, there is the chance of chronicity and a change in biology. All the arguments are in favor of trying to keep patients on drug treatment. And when they wish to stop and discuss that with you, warn them of the consequences of the return of the illness.

**Dr. Hirschfeld:** Taking this into account, how do we deal with patients who are having drug-induced sexual dysfunction?

**Dr. Montgomery:** I would use the same approach: change the drug to one that does not have that problem and also has benefit of long-term treatment, for example, mirtazapine or nefazodone.

**Dr. Thase:** When you recommend that patients take drug holidays, make sure to remind them to take their medication after intercourse (postcoital dosing) at the end of the holiday; they can catch up and lessen the negative effects.

**Dr. Hirschfeld:** How do we differentiate between a "blip" and a recurrence?

**Dr. Rush:** One of the things that I found clinically very useful is to reconstruct what I call "the signature of the episode." For an individual patient, episodes tend to repeat in their own pattern. Some patients have the sleep problem, or lack of energy problem, or they lose interest in sex, or they cannot concentrate. I reconstruct this individual pattern with the patient after the patient gets well, usually together with a family member, and that is a pattern that we are looking at. If a patient has a period of deterioration, but the presentation and progression of symptoms does not follow the pattern, it is not suggesting a recurrence. In that case, I increase the frequency of visits but I do not change the treatment strategy. Another element to look at is disability, the effect of the symptoms on patients' functioning, and sometimes we may see modest symptoms that fit the patient's pattern accompanied with severe disability. In that case, I would suspect an episode. I take into account a lot of the subtle information from the patient and the family members. The key issue is to prepare patients and actually train them over time to recognize "blips," which may occur as a consequence of some events, such as disappointment or death or illness of a close one. I wish we had a peripheral biological marker that we could correlate with depression, as it would help us immensely to guide the treatment.

**Dr. Hirschfeld:** What is the role of psychotherapy and/or clinical management?

**Dr. Rush:** There are some controlled studies in which the same amount of psychotherapy was used; however, talking differently produced different outcomes. These results show that it really matters what you say, how you say it, and when you say it, and that these factors affect outcome. There is also evidence in 5 randomized controlled trials comparing educating patients with depression versus not, showing that the difference between the educated and the noneducated patients is bigger than the difference between drug and placebo. It is a huge effect we need to use appropriately in different phases of treatment and partnering with the patient: early to get adherence, later to get full symptom remission, and further on to get life management and long-term disease control.

**Dr. Hirschfeld:** Could you explain the phenomenon in which people who were born since the Second World War at every age have higher rates of depression at equivalent ages than do people who were born prior to the war?

**Dr. Thase:** Part of it is an honest artifact: as you get older you tend to forget milder episodes of less incapacitating depression early in your life. However, part of it is real. People who live in a simpler world or lead an agrarian life have lower rates of depression. Modern urban life,

the breaking up of the nuclear family, less available social support, greater exposure to drugs and alcohol, and greater exposure to different kinds of trauma evoke human vulnerability to depression. All of these things are more common, and many of these things fall heavier on women in the modern world.

**Dr. Hirschfeld:** However, the gap is not increasing between men and women, and in some age groups such as the younger age groups, it is actually narrowing. There may be a relationship here between some of these phenomena and trauma and stress. There are some animal data showing that if baby rodents are traumatized, they have very profound behavioral effects. If they are pretreated with paroxetine, behavioral effects are substantially ameliorated, suggesting that trauma may be linked to actual morphologic changes in the brain.

**Dr. Rush:** I would like to add that stress clearly alters brain structure and function in very fundamental ways. More recent data suggest that an enriched environment can also do that. It all shows that psychosocial changes affect brain function in areas of the brain that mediate mood and anxiety.