Panel Discussion

Question: *Does the existing data support the use of atypical antipsychotics in the treatment of anxiety disorders?*

Dr. Carson: Despite the limitations of the available published studies, the data strongly suggests that atypical antipsychotics may be effective adjunctive treatment of anxiety disorders, particularly in treatment-resistant patients and patients who are severely ill. Further controlled studies are clearly needed, however.

Question: *Which anxiety disorders would be expected to respond well to augmentation therapy with atypical antipsychotics?*

Dr. Carson: Available data suggests a possible role for atypicals as augmentation therapy for PTSD, GAD, OCD, and possibly panic disorder. With regard to PTSD, there is a need for new forms of treatment because one form of traditional anti-anxiety therapy, namely the benzodiazepines, is not effective and may even exacerbate this illness. There also is a great need for additional treatments of PTSD, because of low rates of response and remission in these patients.

Question: *Would sedating atypical antipsychotics be expected to produce a more rapid onset of anxiolytic effects when used to augment therapy of refractory anxiety disorders?*

Dr. Carson: Not necessarily. Sedation does not necessarily translate into a more rapid onset of anxiolytic effect.

Question: *In the absence of prevention trials, what are the immediate clinical implications of the findings that early-life trauma increases vulnerability to mood and anxiety disorders later in life?*

Dr. Nemeroff: Primary care physicians need to routinely ask their patients about significant traumatic experiences in childhood. Patients with a positive history should then be closely followed for the development of psychiatric illness, and the physician should maintain a high index of suspicion for mood and anxiety disorders in these patients.

Question: *In your study of stress responses in adults, you observed that depressed women with a history of abuse had a cortisol response in the social stress test that was distinct from healthy controls, non-depressed abused women, and depressed women without abuse (Heim et al, 2000). Do patients with both current major depression and a history of childhood trauma represent a unique cohort and if so, what are the implications of this particular clinical presentation?*

Dr. Nemeroff: We do not know the answer to this question, but the combination of depression and early-life adversity may indeed contribute to a distinct neu-

robiological profile. Only well-designed clinical studies will be able to determine if current depression and a history of abuse translate into a distinct subpopulation with its own natural course and response to treatment. It is, however, my view that this is indeed a pathophysiologically distinct subtype that likely explains, in part, the heterogeneity of response in clinical trials of anxiolytic and antidepressant drugs.

Question: *What is the place of the monoamine oxidase inhibitors (MAOIs) in the contemporary treatment of anxiety disorders?*

Dr. Pollack: There is convincing data that the MAOIs are effective treatments for anxiety disorders, particularly panic disorder and social anxiety disorder. However, their side effect liability restricts this class of compounds to second- or third-line treatment. Although many clinicians are convinced that MAOIs may be effective for patients remaining symptomatic despite more commonly used agents, there is little systematic data assessing their use in refractory anxiety disorders. Currently, the MAOIs are rarely used, and some would argue, underutilized, in the treatment of anxiety disorders.

Question: *The data showing that the use of benzodiazepines in the immediate aftermath of a traumatic experience may worsen the outcome in PTSD are interesting and important and also quite different than their role in the treatment of other anxiety disorders. What mechanism underlies the potentially deleterious effect of the benzodiazepines in PTSD?*

Dr. Pollack: Benzodiazepines are sedating, which is likely why clinicians use them in persons who have just had a traumatic experience and are experiencing sleep disturbance or increased anxiety. However, preclinical evidence demonstrates that the benzodiazepines may interfere with the extinction of the fear response, and thus might promote the development and maintenance of PTSD symptoms. However, the data on the clinical impact of benzodiazepines early after a trauma should be viewed only as suggestive at this point, given the small number of patients studied, and further work is needed.

Question: *There appear to be relatively high placebo response rates in many of the SSRI treatment studies of anxiety disorders. What factors contribute to these high rates of placebo response?*

Dr. Pollack: High placebo response rates are an increasing problem in acute studies of many anxiety and mood disorders. A number of possible factors have been implicated including the characteristics of patients entering studies and non-specific supportive factors and therapeutic interventions occurring in the context of clinical trials. Another possible contributing factor is that the course of treatment in many antidepres-

sant studies in anxiety disorders is not sufficiently long for a difference between placebo and drug effect to become apparent. The onset of a clinically significant response to antidepressant treatment often occurs after weeks and sometimes months, which has prompted the widespread use of benzodiazepines for the immediate alleviation of symptoms. Alternate agents are needed that possess the rapid anxiolytic effects of the benzodiazepines without their abuse/dependence, withdrawal, and sedation liabilities.

Question: *Have neuroimaging studies been conducted in elderly persons with anxiety disorders to assess the presence or degree of a failure to regulate normative responses to stress?*

Dr. Salzman: While there are some neuroimaging data beginning to appear in the literature on late-life depression, there is very little imaging data on anxiety disorders in the elderly. We do not know if elderly persons with anxiety disorders are less able than their younger cohorts to mount compensatory mechanisms to life stressors. Studies in this regard are urgently needed.

Question: *What are the considerations for using an atypical antipsychotic agent in an elderly patient with an anxiety disorder who has not responded to conventional anxiolytic/antidepressant treatment?*

Dr. Salzman: In depressed patients, the use of an atypical antipsychotic to augment existing antidepressant therapy may boost the clinical response. However, use of antipsychotics in the elderly requires the use of very low starting doses and slow, gradual upward titration only if necessary. Some of the older atypical antipsychotic agents have been associated with excessive daytime sedation, which is not a desirable feature when treating an elderly person. Agents that do not cause daytime somnolence are desirable.

Question: *Do functional brain scans provide meaningful models of clinical illness?*

Dr. Kilts: A distributed neural processing model is virtually one step removed from the actual clinical presentation of a psychiatric diagnosis. In contrast, while molecular-level studies provide extremely valuable information about mechanism of action, they are significantly more distal to pathological patterns of behavior.

Question: *How can models of distributed neural processing facilitate discovery of new treatments for mood and anxiety disorders?*

Dr. Kilts: As the literature in this field continues to grow, we will begin to recognize discreet patterns of functional brain changes – or pharma-

cologic signatures – that are associated with treatment response. Any new drugs under consideration for monotherapy or as augmentation of existing therapy that appear to match an existing pharmacologic signature of response should be explored further in clinical studies.

Question: *Are there clinical correlates of the aberrant defensive behaviors that you have observed in rhesus monkeys?*

Dr Kalin: We believe that there are many examples of human behavior that can be extrapolated from these animal models. Many persons with an anxiety disorder worry about freezing up– or being unable to speak or react appropriately in stressful situations. In other words, they are overly concerned about being unable to control their arousal and anxiety responses when necessary. Observing individual differences in monkeys' intensity and ability to regulate anxiety-related defensive responses has allowed us to begin to think of human anxiety disorders in relation to issues of adaptive emotion regulation. Different anxiety disorders can be characterized by distinct, but often overlapping, types of maladaptive behaviors. For example, social anxiety disorder occurs in persons who exhibit exaggerated responses to an appropriate situational context, but panic disorder represents an exaggerated response that occurs in an inappropriate context. Individuals with generalized anxiety disorder exhibit prolonged, exaggerated responses to situational stressors, but are characterized by an inability to regulate this response.

Question: *How can the animal models that you described contribute to the process of drug development?*

Dr Kalin: The rhesus monkey likely provides the best model of psychiatric illness because of the close homology between the brains of rhesus and humans and because rhesus monkeys exhibit similarities in behavior, especially facial expressions, physical posturing, and vocalization patterns. The effect of new and established drugs can be studied in the monkey and changes in behavior can be monitored. In addition, neuroimaging studies can be conducted in these animals before, during, and after drug administration to observe the effects on brain metabolic activity. In addition, using positron-emission tomography (PET) scanning with radiolabelled ligands, the effects of drug administration on brain receptor population and occupancy can be assessed. These models could be used to study both acute and chronic administration of antidepressants and anxiolytics. ✤