

Discussion

Audience and Panel Participants: Walter Kaye, Howard Moss, David Comings, Eric Hollander, Dan Hummer, Rita Liu, and Roy King

Dr. Comings: You said that fluoxetine helped the anorexic. What does it do for the bulimic?

Dr. Kaye: The collaborative study suggested that it reduced bingeing and purging. But, again, the effects are modest as few become abstinent, and most of them have some reduction in bingeing and purging. These are all short-term trials, and it is not clear how effective is the long-term administration of antidepressants. It may actually be a more effective drug in anorexia than it is in bulimia.

Dr. Moss: We did an mCPP challenge study of substance abuse in sociopaths, and the responses that we saw were exactly analogous to Dr. Kaye's responses in the weight-recovered anorexics—a blunted prolactin response, euphoric subjective effects. Is it possible that there is sort of a lack of diagnostic specificity in terms of mCPP responses? How can we explain these similarities to disparate conditions?

Dr. Kaye: Yes. I'd say there are two issues here. One is that the anorexics' prolactin response might have been related to their nutritional or their menstrual state.

Secondly, there's nonspecificity to this agent. This agent works on many different serotonergic receptors, as both an agonist and an antagonist, and has actions on other neurotransmitter systems. It's probably one of the best clinically available tools we have now, but it doesn't allow us the amount of specificity that we would really like to begin to tease apart whether different receptors are abnormal in different psychiatric illnesses. We can't tell that at this point.

Dr. Hollander: But, one of the interesting things about that agent is that it has been given to so many different diagnostic populations, and, to some extent, you could make the claim that it brings out symptoms that are specific to the particular disorder itself. So, for example, there was one study in alcoholic sociopaths in which mCPP seemed to stimulate the symptoms that were similar to what they experienced with alcohol. And there was some kind of cross-reactivity in that respect.

Dr. Moss: Our sociopathic substance abusers thought that they were high on a psychedelic drug.

Dr. Hummer: That study with alcoholics was done at several locations. One of the studies was done here in Bethesda by Dr. Markku Linnoila and some other folks in the NIAAA Intramural Program, and they found a blunted prolactin response, as you found, and also a blunted ACTH response. People said they felt like they were high on alcohol, and people who were experienced with cocaine also said they felt like they were high on cocaine, so there are some nonspecific effects.

But, the other thing that we saw, particularly in the Type 1 alcoholics who at the early onset are more sociopathic type of alcoholic, was that they reported a very strong desire to drink alcohol. I'm struck by the fact that you found, with tryptophan, depletion in the bulimics and a strong desire to binge. So, we're sort of getting it both ways here with trypto-phan augmentation, or serotonin augmentation with serotonin agonists, and also with serotonin depletion. Did you have any thoughts on how we might be able to resolve that, or what that might mean?

Dr. Kaye: Yes. I think it brings up the same issue you were probably focusing on with the fluoxetine: How can the same drug have beneficial effects in very different patient populations? The serotonin system has autoreceptors that inhibit this system from firing as well as postsynaptic receptors that affect other systems. When you give fluoxetine or mCPP, they can both inhibit as well as activate the serotonin system. In people with different illnesses, they may have different balances between their serotonin receptors, and therefore respond differently to the same drugs.

Now, that's theoretical. We don't really know that. That needs to be tested in the next generation of studies. Perhaps looking at various serotonin-related genes may be a better way of assessing the serotonin system.

If serotonin is essentially an inhibitory system and you remove that inhibition, you may get many different kinds of behaviors depending on the context of the different illnesses. For sociopaths, it may be euphoria; for anorexia, there may be a reduction of body image, distortion, and things like that. The actual content of the changes may be more related to the illness.

Dr. Hollander: Another way to look at that is to say that you're dealing with the illnesses that may be on different ends of an extreme. There may be more impulsive-style disorders that are associated with pleasure and gratification and compulsive-style disorders that are associated with an anxiety and sort of ego-dystonic feature. But, there is a common theme really for both types of disorders: People have difficulty inhibiting or delaying repetitive behaviors. So, the common mechanism that serotonergic agents may work on is by helping these people be able to delay or inhibit these kind of repetitive behaviors, whether they are pleasurable, ego-dystonic, or anxious.

Dr. Kaye: Absolutely.

Dr. Liu: I'm just wondering, how much of this disorder goes to disorders related to genetics and gender?

Dr. Kaye: Yes. These are disorders that occur almost exclusively in women; for example, 90-95 percent of the people with eating disorders are women. Why is that? I can only guess. There are animal studies, and some human studies, suggesting that serotonergic activity may be related to gonadal steroid activity.

Dr. Liu: A related question then. How comfortable are you to include both genders?

Dr. Gordon: I was going to ask the same question. If you're going to hypothesize this as a model, for example, that either prevents in the case of anorexics or enhances—I wasn't sure whether it was enhancing and whether it's above average—in bulimics, here is a neurochemical mechanism. You're using this as a model, and let's say you find something. Let's say you find overall it relates to that. Well, there's everything to do with the fact that they're females. And, if it doesn't have anything to do with the fact that they're females, why can't you find the same thing in males? What's going on here?

Dr. Kaye: In another study funded by NIAAA, we're finding a very high incidence of alcoholism in the male relatives of bulimic patients. Perhaps because of cultural or gender reasons women who have this trait may develop bulimia instead of alcoholism. Why is that? Who knows?

In the relatives of anorexics, we're finding that they tend to be constrained and perfectionists, and they're not substance abusers.

That's both men and women. So, in fact, there do seem to be patterns of behavior in their families.

Dr. Moss: In addition, testosterone tends to downregulate serotonin receptors in specific regions of the brain. And then they also have something to do with the gender-specific effects that Dr. Kaye was talking about. In particular, for example, testosterone receptors in the amygdala really reduce the amount of serotonergic inhibitory input to the amygdala, which is one potential anatomic location where aggressive behavior is localized. So, there's less behavioral inhibition due to serotonin then.

Dr. King: I'm very fascinated with your finding that the recovered anorexics showed an increase in tendency to prefer symmetry and order. A few years ago, in research we did in schizophrenia, some of the negative symptom schizophrenics had higher CSF 5-HIAA. The 5-HIAA was correlated with the symptom mannerisms in posture, which we interpreted as kind of stereotype-like behavior that's maybe fostered by serotonin activity. We thought of using some of the schizophrenia methodologies in studying your recovered anorexics in terms of cognitive tasks.

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