Commentary on "Vulnerability to Substance Abuse in Eating Disorders" by Kaye and Wisniewski

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SUMMARY

Drs. Kaye and Wisniewski propose an elegant and comprehensive study of serotonergic function in two eating disorder subtypes: anorexia and bulimia nervosa. There is a growing body of literature on the seroto-nergic mediation of behavioral inhibition and affective constriction in both humans and animals. Serotonergic hyperfunction leads to inhibited behavior in animals and anxious and obsessional behavior in humans, while the converse appears to be true with serotonergic hypofunction.

The importance of this work cannot be underestimated both for its inherent heuristic value and for its considerable treatment implications. The numerous common features and high comorbidity in bulimia and alcohol abuse in women (and the lack of this in anorexia) suggest that the study of eating disorders can inform the study of substance abuse. The theoretical bases of the study can be summarized as follows:

1. Decreased serotonin is associated with bingeing, impulsivity, and substance abuse that characterize bulimia nervosa (BN).

2. Increased serotonin is associated with overcontrol, rigidity, restraint, and reduced substance abuse prevalence that characterize anorexia nervosa (AN).

3. Habituation and sensitization to gustatory and other stimulation is reduced in BN.

The proposal has four components comparing AN and BN on:

1. Assessment of mood stability and impulse control using well-known psychiatric instruments.

2. Measures of habituation and startle as assessed by salivary response and galvanic skin response to auditory stimuli, respectively.

3. Feeding behavior and habituation/sensitization to gustatory stimula-tion will be compared using measures of salivation, hunger, fullness, pleasantness, and taste intensity after repeated exposure to foods.

4. Effects of serotonin-affecting drugs by using the acute tryptophan depletion paradigm. The behavioral effects (mood, rigid and overcontrolled behavior, impulse regulation, and feeding behavior) will be assessed following administration (double-blind) of tryptophan-depleting and d-fenfluramine challenges.

Specific methodologies can be summarized as follows:

	Anorexics	Bulimics
Baseline observation	Increased obsession	Decreased obsession
Serotonin metabolite 5-HIAA	Increased	Decreased
Acute tryptophan depletion		Increased impulsivity, substance abuse, bingeing
Augmented serotonin (d-fenfluramine)	Increased obsessions, rigidity, restrictions	

STRENGTHS OF THE PROPOSED RESEARCH

This proposal contains numerous scientific and methodological strengths. Studying serotonergic function in impulsive and impulse-inhibited subtypes of one class of disorders allows both precision and breadth of inquiry. There are considerable implications both for

specific treatment advances and for a general understanding of serotonergic mediation in behavioral and affective pathology. Methodological strengths include:

- comparison of impulsive (BN) and impulse-inhibited (AN) patients on both serotonin depletion and augmentation;

- assessment of the effects of serotonin-depleting (ATD) and serotonin-augmenting (d-fenfluramine) challenges; and

- systematic observation of state/trait naturalistic behaviors in a controlled setting.

WEAKNESSES OF THE PROPOSED RESEARCH

This proposed study is an ambitious and powerful approach to the study of serotonin function in eating disorders. Nevertheless, two major points should be made: The proposed research may be too ambitious for a single study, and there should be more focus on assessment of substance abuse history and substance abuse symptom response to serotonin modulation.

Additional comments and weaknesses have also been noted in an otherwise comprehensive, coherent study with clear focus:

1. More clarification is needed for the specific behaviors affected by serotonin activation.

2. The relationship between eating disorders and substance abuse could be further developed. The suggestion that eating disorders may be a variant of substance abuse may be reductionistic since common features are not equivalent to identity. Nonetheless, the specific commonalities (behavioral, phenomenological, familial, and biological) could be further elaborated. Furthermore, it is not clear if the substance abuse history and family history will be assessed and analyzed. In both the depletion and enhancement study, urge or substance (other than food) craving should be assessed throughout.

3. The relevance of the habituation studies to the serotonin challenge studies is not sufficiently specified. Moreover, habituation to taste seems more a function of sensory-perceptual processes than higher level cognitive functions.

4. Bulimic patients are only assessed after they have recovered from their illness. The authors do not address the question of how their results would vary from a study of acutely ill eating disorder patients.

5. A personal and familial substance abuse history, trauma history, and systematic assessment of Axis II disorders at baseline should be implemented because there is considerable overlap in history of child abuse, personality disorders, and eating disorders.

6. Some of the behavioral ratings appear to rely on visual analog scales that can be easily confounded by poor visual spatial skills.

7. All metabolic blood levels of serotonin probes should be assessed and analyzed because they are important control variables.

8. Side effects to serotonin probes should be systematically assessed to be sure mood changes are not confounded by the side effects.

9. Serotonin challenges are done close together (48 hours), which may cause carryover effects.

10. Baseline differences in mood and behavioral states must be controlled among the subject groups.

11. Multiple analyses pose danger of increased type I error and thus demand data reduction techniques. The use of repeated measures and a discriminant analysis is commendable. However, a multiple regression might be preferable to assess the relative contribution of multiple baseline and independent variables (history and symptom scores) to selected dependent scores (e.g., eating behavior after serotonin depletion). Power analyses need to be done.

ALTERNATE STRATEGIES

The proposal also raises other questions of interest, perhaps to be investigated in later studies.

1. Assess for substance abuse history in subject and family.

2. During acute tryptophan depletion, assess for craving of other substances.

3. Study patients, especially anorexics, in acutely ill phase.

4. Compare anorexics with patients with obsessive-compulsive disorder (OCD) in challenges with mCPP for prolactin response, mood levels, and obsessiveness.

5. Consider the role of other neurotransmitter systems (e.g.,-norepinephrine).

6. Add a treatment component or link with treatment study to see if biological factors can predict outcome.

7. Use serotonin antagonists as a pretreatment agent prior to mCPP administration in anorexia nervosa.

8. Study serotonin and norepinephrine interactions.

9. Consider using mCPP as a serotonin probe to elicit behavioral responses in the anorexic group. The choice of d-fenfluramine over mCPP is worth discussing in more detail.

The similarities and the differences between anorexia and OCD are fascinating. The difference in content between obsessions and compul-sions in anorexics and OCD patients is notable as is the difference in prolactin response to mCPP. While researchers have found blunted pro-lactin response to mCPP in a subgroup of OCD patients, the long-term recovered anorexics show elevated prolactin response in the present proposal. This is an intriguing finding worth further exploration. Furthermore, mood elevation has been found in impulsive but not OCD patients. This proposal reports improved mood and decreased thoughts about body image in anorexics following mCPP; this is surprising as mCPP has produced increased obsessionality in most but not all studies of OCD patients.

The role of noradrenergic regulation is also an important question. Perhaps select noradrenergic challenges with eating disordered patients or use of serotonin antagonists as a pretreatment could be performed at a later date.

Finally, the effect of treatment is an important area to address. If the challenge studies preceded treatment studies, predictors of treatment outcome could be assessed.

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