The ADHD Placebo Effect

Caregivers' perceptions about medications may influence behavior

STIMULANT MEDICATIONS, such as Ritalin and Adderall, are the accepted treatment to stem hyperactivity in children with attention deficit-hyperactive disorder (ADHD) and improve their behavior.

A recent review of research led by UB pediatric psychologist Daniel A. Waschbusch, PhD, suggests that such medication, or the assumption about what medication someone is taking, may produce a placebo effect—not in the children, but in their teachers, parents or other adults who evaluate them.

By Lois Baker

> THE ACT OF ADMINISTERING MEDICATION, OR THINKING A CHILD HAS RECEIVED MEDICATION, MAY INDUCE POSITIVE EXPECTANCIES IN PARENTS AND TEACHERS ABOUT THE EFFECTS OF THAT MEDICATION, WHICH MAY, IN TURN, INFLUENCE HOW PARENTS AND TEACHERS EVALUATE AND BEHAVE TOWARD CHILDREN WITH ADHD.
>
> –Daniel A. Waschbusch, PhD

THE REVIEW, which was published in the April 2009 issue of the *Journal of Developmental & Behavioral Pediatrics,* suggested that when caregivers believed their ADHD patients were receiving ADHD medication, they tended to view those children more favorably and treat them more positively, whether or not medication was actually involved.

"The act of administering medication, or thinking a child has received medication, may induce positive expectancies in parents and teachers about the effects of that medication, which may, in turn, influence how parents and teachers evaluate and behave toward children with ADHD," says Waschbusch.

"We speculate that the perception that a child is receiving ADHD medication may bring about a shift in attitude in a teacher or caregiver. They may have a more positive view of the child, which could create a better relationship. They may praise the child more, which may induce better behavior."

Such a placebo effect in caregivers could have both good and not-so-good results, Waschbusch adds. "If teachers treat children more positively if they think they are on medication, that is a good thing. But if the child's medication is increased because caregivers think it is effective, that may not be a good thing."

Waschbusch, an associate professor of psychology in the Department of Pediatrics, conducts his research in UB's Center for Children and Families. He and his colleagues reviewed existing studies that evaluated whether placebos produce significant changes in children with ADHD and assessed four possible ways placebos could have an effect:

- *Through the child's expectations of a change.* The analysis showed that any change in children's behavior was a direct result of the medication, not the expectation.
- *By producing changes in how caregivers perceive children with ADHD when they think they are on medication.* The researchers determined the studies suggested that this may be a viable mechanism for the placebo effect.
- *By producing changes in how caregivers behave toward children with ADHD who they think are on medication, which in turn, could produce changes in the child.* The analysis supported this hypothesis.
- *Placebos may operate through classical conditioning.* "For example, if a parent routinely gives their child active medication in pill form and then sees their child's behavior immediately improve, they will likely learn to connect administering a pill with improved child behavior," explains Waschbusch. "This learned connection could then be generalized to administering a placebo pill."

Waschbusch says the next step in this investigation could be a study that observes parents and children interacting under three different conditions: after children received a pill with medication, after children received a placebo, and after children did not receive a pill.

"Comparing these conditions would provide information about the effects of actual medication relative to just getting a placebo," he says. BP

William E. Pelham Jr., PhD, UB Distinguished Professor of psychology, pediatrics and psychiatry; James Waxmonsky, MD, UB assistant professor of psychiatry; and Charlotte Johnston, PhD, from the University of British Columbia, are coauthors on the study. When conducting the review, the authors were supported partially by grants from institutes within the U.S. Department of Health and Human Services, the U.S. Department of Education and the Eli Lilly Corporation.

Friendship Influences Eating Behavior

By Lois Baker

A NEW STUDY OF CHILDHOOD OBESITY in the United States has found that some social factors, such as the presence of friends, may put overweight youths at greater risk of overeating.

THE RESEARCH, published in the August 2009 issue of the *American Journal of Clinical Nutrition,* demonstrates that friends may act as "permission givers" on children's food intake.

"These results are important, considering the role of friends as agents of change in childhood and adolescence," says Sarah Salvy, PhD, assistant professor in the Division of Behavioral Medicine, Department of Pediatrics, in the School of Medicine and Biomedical Sciences.

"Being in the company of overweight peers may give [overweight children] permission to eat more or may decrease their inhibitions, increasing what are seen as the norms of appropriate eating, or how much one should eat."

The research involved 23 overweight and 42 normal weight children between the ages of 9 and 15, who were randomized to participate in an eating study with either a friend or an unfamiliar person of a similar age. After randomization, there were 33 friend pairs and 39 "unfamiliar" pairs.

Before taking part in the study experiment, participants listed what they had eaten in the past 24 hours to make sure they hadn't eaten anything during the previous two hours, and rated their hunger level.

Each participant pair spent 45 minutes in a room equipped with games, puzzles and individual bowls of low-calorie, "nutrient dense" baby carrots and grapes, and high-calorie "energy-dense" potato chips and cookies. The children were told they could eat as much or as little as they wanted, but were asked to eat from their own bowls only.

Researchers observed the children via closed-circuit television and recorded their activities. At the end of the session, they weighed the snacks that weren't eaten to determine how much each participant had consumed and to calculate calories.

Results showed that friends who ate together consumed more food than participants who were paired with someone they didn't know, and that friends were more likely to eat similar amounts than participants paired with a stranger.

However, overweight children who were paired with an overweight peer, whether friend or stranger, ate more than the overweight participants who were paired with a normal weight youth.

"These findings indicate that both overweight and normal weight participants eating with a friend ate significantly more than did participants eating in the presence of an unfamiliar peer," Salvy says. "These results are consistent with research in adults, which showed that eating among friends and family is distinctly different than eating among strangers.

"Given the impact of friends on eating behavior, it appears that if we hope to change the growing obesity epidemic among children, friends and family need to be involved," says Salvy. "If the environment in which children live doesn't change, if family meals remain high calorie and overeating is the norm, any progress children may make in their eating behavior won't last."

Salvy currently is investigating the influence of a parent versus a friend on children's and adolescents' eating behavior.

Marlana Howard and Erica Mele, UB bachelor's degree candidates who worked with Salvy, and Margaret Read, UB senior research specialist, also contributed to the study.

The research was supported by a grant to Salvy from the National Institute of Child Health and Human Development. BP

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No Breathing Easy

Childhood asthma worsened by stress and depression

Young people with asthma have nearly twice the incidence of depression compared to their peers without asthma, and studies have shown that depression is associated with increased asthma symptoms and, in some cases, death.

How stress and depression play upon one another to worsen asthma is a lingering question.

By Lois Baker

A new study by UB researchers has shown that depressed children with asthma exhibit a dysregulation of the autonomic nervous system along with increased airway compromise.

It is thought to be the first study to examine pathways linking emotional stress, depressive symptoms, autonomic nervous system dysregulation and airway function in childhood asthma.

The study, which was published in the July 2009 issue of the *Journal of Allergy and Clinical Immunology,* was designed and conducted by Bruce D. Miller, MD, and Beatrice L. Wood, PhD, professors of psychiatry and pediatrics, in collaboration with other UB researchers.

"The autonomic nervous system, or ANS, is composed of two opposing divisions—the sympathetic and parasympathetic nerves, which check one another and thus control critical body functions outside of conscious awareness," explains Miller, chief of the UB Division of Child and Adolescent Psychiatry and senior staff psychiatrist at Women and Children's Hospital of Buffalo, a UB-affiliated teaching hospital. "The ANS is influenced by stress and emotions."

"Children with asthma and high depression symptoms showed a preponderance of parasympathetic over sympathetic nervous system reactivity in the ANS," he continues. "This imbalance within the ANS could explain the increased airway resistance that we found in depressed asthmatic children in our study."

The study, which was supported by grants from the National Institutes of Health, involved 90 children with asthma, aged 7 to 17. Forty-five asthmatic children with symptoms of depression were compared with 45 asthmatic children without symptoms of depression. Both groups viewed scary, sad (death) and happy scenes from the movie *E.T.: The Extraterrestrial.*

All children wore electrodes to collect data on heart and respiratory function, which showed the level of activation and reactivity of the sympathetic and parasympathetic divisions. The researchers assessed airway function before the movie, after the death scene and after the movie.

"The depressed group consistently showed greater parasympathetic activation along with decreased sympathetic activation in response to the emotional provocations—a pattern that would have a detrimental effect on the airways," says Miller.

"In contrast, the group without symptoms of depression showed consistent activation of the sympathetic pathway, which would support better airway function under stress. To our knowledge, this is the first report in the literature to demonstrate an association linking stress, depression and increased airway resistance in asthmatic children."

Results also showed that bias toward parasympathetic reactivity was most pronounced in the children during scenes portraying family distress or loss, death and dying.

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>
> — Bruce D. Miller, MD

"These findings reinforce previous results from our laboratory that associated relational stress within the family with child depression and increased asthma activity," says Wood.

"Although these findings are promising and support our hypotheses," she continues, "we need further studies to replicate and extend these findings and to examine whether treatment for depression reduces shift to the parasympathetic and improves lung function in children with asthma."

The authors believe these findings indicate the importance of screening children with asthma for depressive symptoms, following these children closely and referring them for psychosocial counseling when indicated.

Coauthors on the study were Mark Ballow, MD, an asthma specialist in the UB Department of Pediatrics; ChiunYu Hsu, a student in the UB Neuroscience Graduate Program; and Jung Ha Lim, PhD, formerly a UB postdoctoral student and currently on the faculty at Korea University. BP

Sharpened under Pressure

Short stressful events may improve memory

Chronic stress can adversely affect physical and mental health and have a detrimental effect on learning and emotion. Acute stress, however, may enhance learning and memory.

By Lois Baker

In a study published in the August 18, 2009, issue of the *Proceedings of the National Academy of Sciences* UB scientists have shown that acute stress can produce a beneficial effect on learning and memory through the effect of the stress hormone corticosterone (cortisol in humans) on the brain's prefrontal cortex, a key region that controls learning and emotion.

Working with an animal model, they specifically demonstrated that acute stress increases transmission of the neurotransmitter glutamate and improves working memory, the process by which information is coded into memory, actively maintained and subsequently retrieved for guiding behavior.

"Stress hormones have both protective and damaging effects on the body," says Zhen Yan, PhD, professor of physiology and biophysics at UB and senior author on the study. "This paper and others we have in the pipeline explain why we need stress to perform better, but don't want to be stressed out."

Eunice Y. Yuen, PhD, UB research assistant professor of physiology and biophysics, is the first author on the study.

To test the effect of acute stress on working memory, Yan, Yuen and colleagues trained rats in a maze until they could complete it correctly 60–70 percent of the time. When the rodents reached this level of accuracy for two consecutive days, half were put through a 20-minute forced swim, which served as acute stress, and then were put through the maze again.

Results showed that the stressed rats made significantly fewer mistakes as they went through the maze both four hours after the stressful experience and one day post-stress, compared to the non-stressed rats.

To determine if the corticosterone-induced neuropathway was responsible for the improved memory, as they proposed, researchers injected one group of rats before the stressful forced-swim with a medicinal compound that blocks the pathway and injected another group with saline. Results showed that the saline group, in which the corticosterone neuropathway was not blocked, performed better in the maze than the blocked group.

The researchers also determined that the stressful experience did not increase depression or anxiety-related behavior in the animals.

"It is known that stress has both positive and negative actions in the brain, but the underlying mechanism is elusive," says Yan. "Several key brain regions involved in cognition and emotions, including the prefrontal cortex, have been identified as the primary target of corticosteroid [cortisol in humans], the major stress hormone.

"Our current study identifies a novel mechanism that underlies the impact of acute stress on working memory, a cognitive process depending on glutamate receptor-mediated excitatory signals in prefrontal cortex circuits."

The investigators have expanded this research in several directions. In two other papers that will be published soon, they have identified the key signaling molecules that link acute stress to the enhancement of glutamate receptors and working memory.

"In addition," notes Yan, "we have discovered that chronic stress suppresses the transmission of glutamate in the prefrontal cortex of male rodents, which is opposite to the facilitating effect of acute stress, and that estrogen receptors in female rodents make them more resilient to chronic stress than male rats.

"All these studies should bring new insights into the complex actions of stress in different circumstances that may be applicable to humans in the future," she notes.

Wenhua Liu, PhD, research scientist, and Jain Feng, PhD, associate professor, both in the UB Department of Physiology and Biophysics, are coauthors on the study, as is Ilia N. Karatsoreos, PhD, and Bruce S. McEwen, PhD, from the Rockefeller University. BP

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