



Bulletin Board

This comparison of lithium versus divalproex and placebo in acute-phase mixed or manic episodes of symptomatic bipolar I disorder in children and adolescents gives hope for new effective treatment options

Efficacy of lithium versus divalproex in children and adolescents with bipolar I disorder established in new study

A recent presentation at the American Academy of Child and Adolescent Psychiatry (AACAP) 55th Annual Meeting has offered insight into the use of lithium and divalproex in the management and treatment of children and adolescents with bipolar I disorder.

Divalproex is an efficacious treatment for mixed or manic episode in children and adolescents with bipolar I disorder and is already in use, but the researchers established that additional controlled trials were required to demonstrate the safety and efficacy of lithium in the management and treatment of these children.

Lithium is a prototype mood stabilizer for treating adult bipolar disorder, but it is not yet US FDA-approved for use in children younger than 13 years of age.

Previous studies have raised the profile of lithium in the treatment of the bipolar I due to the current lack of drugs able to cure all aspects of the disorder. It is thought that finding out more about lithium and how it affects children could bring doctors closer to managing the devastating condition.

The lead investigator, Robert Findling, University Hospitals, Case Medical Center, Cleveland, Ohio, USA, presented the study results on October 31, 2008 at the AACAP 55th Annual Meeting.

This study's main objective was to compare the efficacy of lithium, divalproex and placebo for treatment of acute-phase mixed or manic episodes of symptomatic bipolar I disorder in children and adolescents.

A total of 150 patients aged from 7 to 17 years, with bipolar I disorder were randomized to double-blind treatment with lithium, divalproex or placebo in a 2:2:1 ratio. Primary outcome measure for the study included, Young Mania Rating Scale (YMRS) and the Clinical Global Impressions – Improvement (CGI-I) scale. Each of these were measured weekly in the children.

The results indicated that divalproex appeared efficacious in the acute phase, and there was a trend in the same direction for lithium. By week 8, the mean weekly YMRS scored showed that divalproex was significantly more effective than the placebo and significantly more effective than lithium. Divalproex peaked at week 4, and by week 8, it had the lowest score on the YMRS.

The researchers concluded that divalproex is efficacious for the treatment of children aged 7–17 years with bipolar I disorder. The authors note that additional controlled trials are needed to demonstrate the efficacy of lithium in this population. Although lithium had a definite trend towards efficacy, it did not clearly separate from placebo on the primary outcome measures and continuation/re-randomization results are still pending, according to the researchers.

Source: The efficacy of lithium versus divalproex in children and adolescents with bipolar I disorder (Abstract 33.2). Presented at: *The American Academy of Child and Adolescent Psychiatry 55th Annual Meeting*, Chicago, IL, USA, October 31 2008.

Pediatric HEALTH

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in brief...

Growth patterns and obesity development in overweight or normal-weight 13-year-old adolescents: the STRIP study.

Lagström H, Hakanen M, Niinikoski H et al.: *Pediatrics* 122(4), E876–E883 (2008).

Studied childhood growth patterns and development of overweight in children who were overweight or normal weight at 13 years of age, as part of a prospective atherosclerosis-prevention trial. A total of 1062 children were randomly assigned to an intervention group (n = 540) receiving biannual fat-oriented dietary counseling or to a control group at 7 months of age; height and weight of the child and their parents were monitored annually. Results indicated that in overweight girls, the annual weight gain increased from 2.8 kg in the third and fourth year of life to 7.5 kg during the 12th year of life. In normal-weight girls, weight gain range from 2.1 to 4.8 kg during the same period. Weight gain was similar in overweight and normal weight boys until 5 years but increased from 3.5 to 7.9 kg in overweight and from 2.6 to 5.5 kg in normal-weight boys. The results concluded that girls became overweight by the age of 5 years, whereas the boys only after 8 years of age. Parental BMI and steep weight gain in early childhood indicate markedly increased the risk for becoming overweight.

Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety.

Walkup JT, Albano AM, Piacentini J et al.: *N. Engl. J. Med.* (2008) (Epub ahead of print).

This randomized, controlled trial studied the effect of the relative and combined efficacy of cognitive behavioral therapy and selective serotonin-reuptake inhibitors. A total of 488 children between the ages of 7 and 17 years who had a primary diagnosis of separation anxiety disorder, generalized anxiety disorder, or social phobia were assigned to 14 sessions of cognitive behavioral therapy, sertraline, a combination of sertraline and cognitive behavioral therapy or a placebo drug. Categorical and dimensional ratings of anxiety severity and impairment at baseline and at weeks 4, 8 and 12 were established. The percentages of children who were rated as very much or much improved on the Clinician Global Impression–Improvement scale were 80.7% for combination therapy, 59.7% for cognitive behavioral therapy and 54.9% for sertraline. All therapies were superior to placebo and combination therapy was superior to both monotherapies. Results on the Pediatric Anxiety Rating Scale also reflected this magnitude and pattern of response; combination therapy had a greater response than cognitive behavioral therapy. The authors conclude that both cognitive behavioral therapy and sertraline reduced the severity of anxiety in children with anxiety disorders; a combination of the two therapies had a superior response rate.

Exposure to dogs in infancy could reduce atopic dermatitis and wheezing in childhood

Researchers now believe that exposure to family pets, such as dogs, in infancy could trigger changes in the development of the immune system and reduce wheezing and atopy.

This response is thought to be irrespective of exposure of the immune system to other allergens such as dust.

“...exposure to family pets, such as dogs, in infancy could trigger changes in the development of the immune system...”

The study, led by James Gern from the University of Wisconsin-Madison, WI, USA, aimed to determine the impact of childhood exposure to pets on the immune system. A total of 275 children at increased risk for developing allergic disorders were studied and assessed for blood cell cytokine response and atopy as well as pet ownership. At-risk children required at least one parent of each child to have respiratory allergies or a family history of confirmed asthma.

The team assessed that at birth, 35% of children were exposed to dogs and 29% were exposed to cats in their home. At 3 years of age these figures has dropped slightly to 32 and 25% of children being exposed to dogs and cats, respectively. Samples of settled dust from the participating children's bedrooms was also taken and examined for levels of Can f 1, Fed d 1, endotoxin, ergosterol and muramic acid.

“At-risk children required at least one parent of each child to have respiratory allergies...”

The results revealed that exposure to dogs at birth was associated with a significantly lower prevalence of atopic dermatitis at 3 years of age – a prevalence

of 12% in exposed compared with 27% prevalence in nonexposed children. This decrease was also observed in wheezing, with a 10 versus a 36% prevalence in nonexposed and exposed children, respectively.

“...exposure to dogs at birth was associated with a significantly lower prevalence of atopic dermatitis at 3 years of age...”

The results also revealed that dog exposure at birth did not have an effect on the prevalence of dog sensitization. Also, The levels of Can f1 in bedroom dust were associated with IL-10 and IL-13 responses at age 1 year and IL-5 and IL-13 responses at age 3 years.

The author also note that rates of atopic dermatitis and wheezing at 3 years were relatively high among children exposed to a dog after birth, at 23 and 42%, respectively and debate remains as to the importance of the timing of exposure, and the underlying mechanisms are still being explored.

“...debate remains as to the importance of the timing of exposure...”

“In summary, early childhood is a period of rapid immunological development, and these findings indicate that exposure to dogs can influence this process in a manner that is associated with reduced atopic dermatitis and wheezing in predisposed individuals,” the team says.

Source: Bufford JD, Reardon CL, Li Z et al.: Effects of dog ownership in early childhood on immune development and atopic diseases. *Clin. Exp. Allergy* 38(10), 1635–1643 (2008).

Use of paracetamol in the first year of life increases risk of asthma, rhinoconjunctivitis and eczema in children

Researchers have discovered evidence for a link between the use of paracetamol in the first year of life or in later childhood and an increased risk of asthma, rhinoconjunctivitis (RC) and eczema at 6–7 years of age.

More than 200,000 children from 73 centers in 31 countries were analyzed in a study conducted as part of Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) program to investigate the association between paracetamol consumption and asthma. Children and their parents were asked to complete questionnaires regarding symptoms of asthma, conjunctivitis and eczema. Questions about several risk factors including the use of paracetamol in the first year of life and the frequency of use in the last 12 months were also asked.

“Use of paracetamol in the first year of life, and in later childhood, is associated with risk of asthma, RC and eczema at age 6–7 years. We suggest that exposure

to paracetamol might be a risk factor for the development of asthma in childhood,” the authors wrote.

“...use of paracetamol for fever in first year of life was associated with an increased risk of 46% of asthma symptoms...”

The results suggested that the use of paracetamol for fever in first year of life was associated with an increased risk of 46% of asthma symptoms in children 6–7 years of age. Recent and current use was associated with a dose-dependent risk of asthma symptoms, with medium use increasing risk by 61% and high-dose increasing risk by over three times.

Paracetamol use was also associated with increased risk of severe asthma symptoms; when used in the first year of life and with rhinoconjunctivitis, and eczema at age 6 to 7 years. The authors suggested

that exposure to paracetamol might be a risk factor for the development of asthma in childhood. There was an associated increased risk of RC by 48% and eczema by 35%.

The authors added, “we stress the findings do not constitute a reason to stop using paracetamol in childhood. Paracetamol remains the preferred drug to relieve pain and fever in children. However the findings do lend support to the current guidelines of the World Health Organization, which recommend that paracetamol should not be used routinely, but should be reserved for children with a high fever.”

Source: Prof. Richard Beasley Tadd Clayton, Prof. Julian Crane: Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase III of the ISAAC programme. *Lancet* 372(9643), 1039–1048 (2008).

Second-hand smoke could affect children more than adults

There is new evidence suggesting that the carbon monoxide levels of children exposed to second-hand smoke are often similar to that of adults who actively smoke.

Levels of carbon monoxide also appear to be frequently higher than levels in adults exposed to second-hand smoke. These findings were presented at the Annual Meeting of the American Society of Anesthesiologists.

The research group lead by Branden Yee, Anesthesiology department, Tufts Medical Center, Washington, MA, USA, enrolled 200 children between the ages of 1 and 12 years to assess their level of carboxyhemoglobin (carbon monoxide bound to the blood).

Carbon monoxide binds to blood 200 times more easily than oxygen, and created carboxyhemoglobin, which is

unable to deliver oxygen to body tissue and organs such as the brain and heart and potential consequences of long-term, low-level exposure include changes in the heart and lung tissue. Household environmental factors such as stoves, heaters and automobiles are potential sources of carbon monoxide exposure, but the most likely source of elevated carboxyhemoglobin overall is second-hand cigarette smoke.

Yee discussed that the younger the child, the greater the potential level of exposure. “The physiology of children – especially the youngest – is different from that of adults,” said Dr Yee. “Children breathe in a greater amount of air per body weight compared to adults.”

The researchers stressed the importance of education in helping to change parents’ smoking habits and especially those around

children; this could be achieved by physician intervention and new technology.

“...the younger the child, the greater the potential level of exposure.”

“The simple, noninvasive device we used to test exposure may encourage health care providers to ask further questions of children and their parents regarding smoking habits,” added Yee. “Personalized education coupled with the act of physically showing a parent the carboxyhemoglobin measurement in his or her child’s blood may provide a graphic and concrete message to that parent.”

Source: Presentation at the American Society of Anesthesiologists. <http://www.asahq.org>