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CLiPPs

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CLiPPs (**C**urrent **L**iterature in **P**ediatric **P**sychosomatics) *is a pertinent article review through the AACAP Physically Ill Child Committee for psychosomatic clinicians from a range of medical science journals and literature. We are very excited for our inaugural issue is finally here and have already begun working on our Summer 2016 edition.*

Inflammation and Predictors of Depression in Pediatric IBD Patients

Background and Objective: The incidence of Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel diseases (IBD), is increasing among youth in the U.S. with the onset of symptoms before age 18 approximately 25-30%. CD is associated with more systemic inflammation than UC. Depression is increasingly recognized in the population with IBD and four symptom clusters namely, **somatic-affective, low self-esteem, suicidality, and anhedonia** are identified to describe the psychopathology of clinical depression. Each cluster seems to be linked to a different etiology. The **aim** of this study was to identify depressive symptoms related to inflammatory disease activity in youth with Crohn's disease (CD).

Methods: Youth (ages 9-17) with CD (n = 765) were recruited at Boston Children's Hospital and Children's Hospital Pittsburgh. Children's Depressive Index (CDI) was used for initial screening and a **score of ≥12** was considered to represent **clinically significant depressive symptoms (CSDS).** Disease activity was measured using the **Pediatric Crohn's Disease Activity Index (PCDAI**) which is a multi-item instrument consists of four general fields: history, physical examination, growth parameters, and common laboratory tests. Data regarding **demographics**, **inflammatory markers** (C-reactive proteins, cytokines, ESR, etc.), **IBD medications** (steroids, biologics, immunomodulators), and **prior surgery** (ostomies, etc.) were obtained from the EMR.

Results: The study recruited 550 CD patients with equal gender distribution and an average age of 14.4 years. Mean PCDAI score was 13.6, **indicating mild disease.** Score of 41% **indicated to be in remission** and out of the remaining 59%, one third had mild symptoms, while 6.4% had moderate, and 7.3% noted to have severe disease. At baseline, 38.8% met criteria for CSDS, of whom 9.4% had prior surgery, 12.3% ostomy, and 28.1% were on corticosteroids. **Somatic-affective symptoms** presentation was significant in the females, patients on corticosteroids, those with elevated PCDAI scores. Elevated ESR, or lower hematocrit or albumin was also related to this category of symptoms. Similarly, **anhedonia** was linked with elevated PCDAI subjective and objective lab scores, ESR, CRP,

and those on corticosteroids. **Low self-esteem and suicidality** correlated with the subjective PCDAI subscale ($P < 0.01$), but NOT with inflammatory markers.

Conclusions: Inflammatory markers (low hematocrit or low albumin, and with high ESR), corticosteroid therapy, female gender and disease activity are **significant predictors of somatic-affective symptoms and anhedonia** in youth with IBD. Social support, coping styles, childhood trauma, and disease course should be evaluated as **potential predictors** of these clusters. Identification of symptom profiles can **guide treatment** of comorbid IBD and depression. Even if somatic-affective symptoms stem from inflammation, **referral to psychotherapy** can improve symptoms more rapidly.

Take-away: Somatic-affective depressive symptoms and anhedonia clusters are highly correlated in youth with IBD and could be predicted by the presence of inflammatory markers and active disease. Early detection and referral to psychotherapy may have positive outcome in spite of the inflammatory origin of symptoms. Low self-esteem and suicidality are not correlated with inflammatory markers.

References:

1. Szigethy EM, Youk AO, Benhayon D, et al. Depression Subtypes in Pediatric Inflammatory Bowel Disease. *J Pediatric Gastro Nutrition* 2014; 58(5):574-581.
2. Hyams, J., et al. Evaluation of the pediatric crohn disease activity index: a prospective multicenter experience. *J Pedi Gastro Nutrition* 2005; 41(4): 416-421.
3. Reed-Knight B, Lobato D, Hagin S, et Al. Depressive symptoms in youth with inflammatory bowel disease compared with a community sample. *Inflam Bowel Dis* Apr 2014 (6):614-21.
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Reviewer: Khalid I. Afzal, MD, DFAACAP, Assistant Professor, The University of Chicago, Chicago, IL.

Source: Levine A, Keljo D, DeMaso D, et al. Inflammatory Versus Non-inflammatory Predictors of Specific Depressive Symptoms in a Large Pediatric Cohort with IBD. Inflam Bowel Dis, Mar 2016; 22, Suppl 1: S6. Link here.

Neurocognitive Late Effects in Childhood ALL Survivors Treated with Chemotherapy

Background and Objective:
With improving survival rates for childhood ALL, long-term effects of CNS-directed therapy has been of increased concern. CNS-directed radiotherapy is now rarely used due to its adverse effects on brain development and intellectual functioning; it has largely been replaced by chemotherapy with methotrexate. Early studies have suggested that while chemotherapy-based treatment does not have

as great an impact on cognitive functioning as radiotherapy, and does not appear to affect general intellectual ability, there may be negative effects on specific neurocognitive domains. This study conducted in Norway aimed to examine neurocognitive function in very long-term childhood ALL survivors treated with chemotherapy, and to investigate associations between neurocognitive performance and individual treatment load.

Methods:
One hundred and twelve adult ALL survivors diagnosed before age 16 and treated with chemotherapy only, and 100 comparison peers, underwent neuropsychological tests examining processing speed, executive functions, working memory, and verbal learning and memory. Individuals' treatment regimens (cumulative doses of cytostatic agents) were extracted from their medical records and compared with poor neuropsychological performance.

Results:
Mean IQ between survivors and the comparison group was not significantly different. In specific neurocognitive domains, however, specifically processing speed, executive function, and working memory, survivors performed significantly more poorly. Rates of poor cognitive performance (greater than 1.5 standard deviations below the control mean) were 22% for processing speed, 31% for executive function, 34% for working memory, and 16% for verbal learning and memory. There was no association between poor neurocognitive performance and cumulative doses of chemotherapy, age at diagnosis, or gender.

Conclusions / Commentary:
This study provided long-term analysis supporting established concern that chemotherapy for ALL may cause specific neurocognitive impairments, raising important issues regarding informed consent for patients considering this treatment. Interestingly, there did not appear to be a dose-related association between chemotherapy and specific impairments. This raises the question of whether there may be other factors contributing to these impairments (e.g. corticosteroids, cancer itself, trauma?). It also underscores the need for additional research regarding protective factors that could counter neurocognitive impairment.

Take-away:
Specific neurocognitive impairment late effects are highly prevalent in survivors of childhood ALL. Additional research is needed to clarify the mechanism of these impairments, and to identify protective factors to help ameliorate the neurocognitive effects of this disease and its treatment.

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1. Campbell LK, Scaduto M, Sharp W, Difton L, Van Slyke D, Whitlock JA, Compas B. A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia. *Pediatr Blood Cancer* 2007; 49:65-73.
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3. Castellino SM, Ullrich NJ, Whelen MJ, Lange BJ. Developing interventions for cancer-related cognitive dysfunction in childhood cancer survivors. *J Natl Cancer Inst.* 2014;106(8) pii:dju186.

Reviewer: Rebecca Marshall, MD, MPH, Oregon Health & Science University, Portland, OR.

Source: Kanellopoulos A, Andersson S, Zeller B, Tamnes CK, Fjell AM, Walhovd KB, Westlye LT, Fossa SD, Ruud E. Neurocognitive Outcome in Very Long-term Survivors of Childhood Acute Lymphoblastic Leukemia after Treatment with Chemotherapy Only. *Pedi Blood Cancer* 2016;63:133-138. Link here.

Pharmacotherapy in Anorexia Nervosa and Bulimia Nervosa

Background and Objectives: The objective of the paper was to review the scientific evidence for both efficacy and safety of pharmacotherapy in children, adolescents and adults with an eating disorder.

Methods: The authors conducted a search of two databases (Medline and PsycINFO) for randomized controlled trials, open trials or case reports on pharmacotherapy of Anorexia Nervosa (AN), Bulemia Nervosa (BN) and Binge Eating Disorder (BED) from 1960 to May 2010. Other systemic reviews, meta-analysis and NIDA and APA guidelines were also included. This summary is focused on medications that had some evidence in adolescents and children.

Results:
AN: As for SSRIs, two parallel studies for fluoxetine 20-60 mg vs. placebo showed not only no difference in weight gain or ED symptoms but also no difference in associated depression, anxiety and obsessive-compulsive symptoms. Two separate one year relapse prevention studies gave conflicting results, one showing some benefit (Kaye et. al 2001) the other showing no benefit (Walsh et. al 2006) in weight restored patients. A retrospective study in adolescents showed no benefit in AN with fluoxetine, fluvoxamine or sertraline when compared to unmedicated adolescents. As for atypical antipsychotics, olanzapine had the most evidence with three small randomized controlled trials in adults and several small case series in children and adolescents showing improvements in depression, anxiety, agitation, anorexic ruminations as well as weight gain. The authors also concluded that typical antipsychotics, tricyclic antidepressants and appetite enhancers e.g. cyproheptadine or bisphosphonates / estrogen for osteopenia demonstrated no benefit and were not recommended.

BN: Fluoxetine 60 mg/day has robust evidence in randomized controlled trials in adults and an open trial in adolescents for reduction of bingeing and purging as well as core eating attitudes and associated depression symptoms. Similarly, a randomized controlled trial for sertraline 100mg/day showed efficacy in reducing binge/purge episodes while fluvoxamine yielded mixed results.

Conclusion/Commentary: Evidence base for use of medications in children and adolescents with eating disorders is extremely limited. No randomized controlled trials exist in this population, leaving

the burden of evidence on case series or adult trials. For AN, adult trials are limited by small sample sizes and high dropout rates. This review concludes that pharmacotherapy research in ED has a long way to go and novel pharmacological compounds targeting dietary restraint or binge eating as well as maladaptive weight-shape cognitions are needed.

Take Away: SSRIs do not offer benefit for core AN symptoms OR associated depression and anxiety in underweight patients. Therefore, the focus of treatment should be evidence based psychotherapy and weight restoration. Olanzapine has shown benefit in small studies for weight gain and ED cognitions. Fluoxetine and sertraline have evidence-based benefit in reducing core eating disorder symptoms and associated psychopathology in BN.

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1. Holtkamp K et al. A retrospective study of SSRI treatment in adolescent anorexia nervosa: insufficient evidence for efficacy. *J Psychiatric Research* 2005; 39, 303-310.
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Reviewer: Finza Latif, M.D; Children's National Health System, Washington, D.C

Source: Flament, F, Bissada H, Spettigue, W. Evidence-based pharmacotherapy of eating disorders.Int J Neuropharm 2012; 15, 189-207.

CLiPPs Feedback

We appreciate any feedback for our young, developing review series.

CLiPPs is edited by Chase Samsel, MD, Boston Childrens Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115. All critical summaries are written by the designated reviewers.

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