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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 in Children and Adolescents with Neuropsychiatric Disorders

Background and Objective: Inflammation is well established as a factor in the pathogenesis of chronic medical diseases that are highly co-morbid with psychiatric disorders. There is great evidence supporting the link between inflammation and major depressive disorder in adults, and more research is also linking inflammation and MDD and other psychiatric disorders in children. The purpose of the review was to summarize the evidence regarding inflammation and psychiatric disorders in children and adolescents.

Methods: A systematic review of the literature on inflammation, neuropsychiatric disorders in children and adolescents was performed via MEDLINE looking at all studies from 1946 to August 2013. Studies were included if the pro-inflammatory markers (PIMs) in children and or adolescents with neuropsychiatric disorders were measured.

Results: 67 studies, involving 3,952 youth, were included in the final analysis and review, but the MEDLINE search yielded 667 citations. Evidence for the pro-inflammatory state was found to be strongest in autism spectrum disorders (ASD). IFN-γ was elevated or showed a trend toward elevation in many of the studies compared to controls. Some of the other pro-inflammatory markers were inconsistent with some studies show increases and others showing no difference between controls. The data also demonstrated increases in PIMs in children and adolescents with MDD, Bipolar Disorder, PTSD, OCD, Tourette's Disorder, ADHD, and Schizophrenia. The data was inconsistent across the many studies. The findings in youth with MDD, Bipolar Disorder, and PTSD seem to be similar and equivocal to the adult literature in this area. Specifically, IL-6, IFN-γ, IL-2, CRP, and TNF-α were seen to be elevated in both children and adolescents with the above disorders, but also in first degree relatives of those with the above disorders.

Conclusions/Commentary: There is preliminary evidence for elevated markers of inflammation in children and adolescents with neuropsychiatric disorders, specifically ASD, MDD, Bipolar Disorder, and

PTSD. Pro-inflammatory markers are unlikely to serve as diagnostic biomarkers because of the non-specific nature, but they may serve as essential markers of illness activity and potential treatment response. More research needs to be completed with larger, prospective studies to appreciate the goal of inflammatory markers apprising clinical practice.

Take-away: Inflammation and neuropsychiatric disorders in children and adolescents appear to have a relationship similar to that in adults, with elevated PIMs, but more research needs to be done to truly understand the implication.

References:

1. Tonhajzerova, I, Ondrejka, I, Mestanik, M. et al. Inflammatory activity in autism spectrum disorders. Advances in experimental medicine and biology. 2015; 861:93-98.
2. Fond, F., d'Albis, MA., Jamain, S. et al. The promise of biological markers for treatment response in first-episode psychosis: a systematic review. Schizophrenia Bulletin. May 2015; 41(3): 559-573.

Reviewer: Nicole A. Mavrides, M.D., University of Miami/Jackson Memorial Medical Center, Miami, FL.

Source: Mitchell, RH, MD, Goldstein, BI. Inflammation in Children and Adolescents with Neuropsychiatric Disorders: A Systematic Review. Journal of the American Academy of Child and Adolescent Psychiatry. March 2014; 53(3): 274-296. Pubmed link can be found here.

Atypical Antipsychotics in Pediatric Delirium

Background and Objective: Delirium can occur in seriously ill patients of all ages and has been associated with longer hospital stays and high morbidity and mortality in children and adolescents. Its management relies on identifying and treating the underlying cause(s). Medication can be helpful in addressing behavioral dysregulation, psychosis, and cognitive impairment. There are no double-blind randomized or placebo-controlled clinical trials and no FDA approved agents for delirium treatment. Atypical antipsychotics have been used as a first-line approach for managing delirium symptoms in adults. This retrospective study describes delirium in a pediatric cohort, identify underlying etiology, and describe use of antipsychotics to address symptoms of delirium.

Methods: Retrospective pharmacy record review and retrospective calculation of Delirium Rating Scale-Revised-98 scores were completed for patients age 1-18 years old seen in a 24 month period. DRS-R98 scores were calculated at time when the antipsychotic was started and again when antipsychotic was stopped.

Results: During the 2 years of study, 110 patients were included. 61 children were ages 1-12yo and 49 were ages 13-18yo. 78 patients were treated with olanzapine, 13 with risperidone, and 19 with quetiapine. No significant differences existed amongst the three groups in terms of age, length of treatment, or response. 75 of the 110 patients had 2 DRS-R98 scores available and there was a

significant decrease in the mean score without significant side effects. Initial scores ranged 11-32 and final scores ranged 1-13. Sleep, intubation, and speech status influenced ability to completely score the DRS-R98. In drug-induced delirium, higher dosages of antipsychotics were used. Side effects described included one case of mild dystonia with olanzapine initiation. No cardiac arrhythmias developed. Four patients died of their underlying medical condition during the study period.

Conclusions/Commentary: This study describes a cohort that had significant improvement of delirium symptoms (using the DRS-R98 to rate severity) while taking olanzapine, risperidone, or quetiapine with low incidence of side effects (1/110). We cannot compare safety and efficacy of these three agents in delirium given the study design. Other limits of the study included its retrospective descriptive design with no randomization, unequal medication group sizes, and no placebo-control group. DRS-R98 ratings were not blinded and the DRS-R98 requires a higher baseline cognitive function than found in younger patients. Improvement of delirium symptoms cannot be attributed to antipsychotic alone and could be reflection of improvement of multiple factors (med condition, removal of deliriogenic agents, environmental milieu) in synergy. Metabolic syndrome may not have occurred due to being a seriously ill and likely under-nourished population with a brief duration of exposure to an atypical antipsychotic. Oral administration of the medications can be used; none of the children required intravenous or intramuscular antipsychotic administration.

Take-away: Atypical antipsychotics can be safe and effective in pediatric delirium of multiple etiologies. Prospective and placebo controlled studies of antipsychotic use in pediatric delirium are needed.

References:

1. Joyce C, Witcher R, Herrup E, et al. Evaluation of the Safety of Quetiapine in Treating Delirium in Critically Ill Children: A Retrospective Review. Journal of Child and Adolescent Psychopharmacology (2015). 25:666-670
2. Turkel SB, Jacobson JR, Tavare JC. The Diagnosis and Management of Delirium in Infancy. Journal of Child and Adolescent Psychopharmacology (2013). 23:352-356
3. Smith HAB, Gangopadhyay M, Goben CM, et al. The Preschool Confusion Assessment Method for the ICU: Valid and Reliable Delirium Monitoring for Critically Ill Infants and Children. articles that illustrate previous evidence or complementary for the brief discussion. Critical Care Medicine. 2015 Nov 12 [Epub ahead of print].

Reviewer: Maalobeeka Gangopadhyay, M.D., NewYork-Presbyterian Morgan Stanley Children's Hospital, Columbia University Medical Center, New York, NY.

Source: Turkel SB, Jacobson J, Munzig E, Tavare CJ. Atypical Antipsychotic Medications to Control Symptoms of Delirium in Children and Adolescents. Journal of Child and Adolescent Psychopharmacology (2012) 22: 126-130. Pubmed link can be found here.

Cost and Effectiveness Comparison of Pregabalin, Gabapentin, Duloxetine, and Despiramine in Painful Diabetic Neuropathy

Background and Objective: Painful diabetic neuropathy (PDN) affects nearly half of diabetic patients in their lifetime. Multiple short-term studies have recently been comparing the efficacy and cost-effectiveness of tricyclic antidepressants, gabapentin, pregabalin, and duloxetine for PDN and herpetic neuralgia. These are the first line treatments along with secondary options including opiates, carbamazepine, lidocaine patches, and capsaicin. The American Academy of Neurology and American Academy of Physical Medicine and Rehabilitation recently recommended pregabalin (PRE) as the first-line treatment for PDN. Many clinicians are confused by the ongoing lack of consensus of first-line treatment for neuropathic pain from conflicting information. Less than 1/3 of patients with PDN find a stable regimen in the first year after diagnosis and often switch treatments due to cost, adverse reactions (AE), and inadequate reduction in pain. This study aims to evaluate the long-term efficacy and cost-effectiveness of between PRE, duloxetine (DUL), gabapentin (GABA), and despiramine (DES).

Methods: 10,000 patients were accumulated from clinical trials and case series ranging between 3 months and 5 years involving the four medications of interest. Pooled patients were individually analyzed in microsimulation analytic models to evaluate for cost (hospital and office visits and prescription costs) and effectiveness (quality-adjusted life-years/QALYS). Cost was calculated from 2013 Red Book averages for medicine in middle dosing in clinicians trials and Centers for Medicaid and Medicare Physician Fee Schedules for office and hospital visits. Separated and combined cost-effectiveness was derived from these data.

Results: DUL was the most cost-effective option 56% of the time, DES in 29%, GABA in 14.4% and PRE in 0.1%. Starting with PRE cost more and was less effective than starting with DUL, primarily because of AE and non-adherence. PRE was the most cost-effective option when it was not stopped due to AE and willingness to pay for it was not an obstacle. When willingness to pay was lowest, DES was the most cost-effective option. No psychiatric factors were studied.

Conclusions/Commentary: Many pain and palliative care clinicians are interested in SNRIs for comorbid pain and depression. Worry about (COI) and lack of pharmacoeconomic data in existing research has kept many clinicians from prescribing DUL. Based on these results, clinicians may consider DUL and DES as first-line monotherapies for cost and effectiveness over GABA and PRE. Limitations include few studies with adherence results in the pooling. Strengths included data evaluating payer and patient cost and effectiveness amongst monotherapies of varying expense. None of the authors had disclosures from Eli Lilly (Cymbalta/Duloxetine) and one senior author had a disclosure from Pfizer (Lyrica/Pregabalin). There is less concern for conflicts of interest (COI) given PRE did not fare well in this study. No estimates of the difference between DUL and other SNRIs can be made.

Take-away: This along with many other recent papers showing similar results may increase prescription of DUL in non-psychiatrists. Research measuring improvements in anxiety and depression as mediators of neuropathic pain cost and effectiveness is needed.

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1. Lunn, MP, Hughes RA, Wiffen PJ. Duloxetine for treatinng painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014 Jan 3;1.
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3. Zhao Y, Sun P, Watson P, Mitchel B, Swindle R. Comparison of medication adherence and healthcare costs between duloxetine and pregabalin initiators amongst patients with fibromyalgia. Pain Pract 2011;11:204-216.

Reviewer: Chase Samsel M.D., Boston Childrens Hospital and Dana-Farber Cancer Institute; Harvard Medical School, Boston, MA

Source: Bellows, B.K, Nelson, R.E., Oderda, G.M., LaFleur, J. Long-term cost-effectiveness of initiating treatment for painful diabetic neuropathy with pregabalin, duloxetine, gabapentin, or desipramine. Pain 2016 Jan; 157(1): 203-213. Pubmed link can be found here.

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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