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CLiPPs

LATE SPRING 2018

CLiPPs (**C**urrent **L**iterature in **P**ediatric **P**sychosomatics) *is a pertinent article review from a range of medical science journals and literature from the AACAP Physically Ill Child Committee for consultation/liaison psychiatrists. We are very excited our 6th edition is here. If you did not get previous editions, we are happy to re-forward them.*

We are excited to present our belated spring edition and thank our contributors for the past year. Look out for the invite for the next academic year's board and contributors following this email.

This issue highlights a number of important child and adult C-L studies: a negative study/failed trial of an immunotherapeutic, a DB-RCT on hydrocortisone for steroid-induced mood disorder, a study showing the pediatric C-L elements associated with parent and patient satisfaction, and two adult RCTs for delirium - one on dexmedetomidine and the other one risperidone and haloperidol vs none.

All of these studies highlight the need for more psychiatric input into our own literature, excitement and concern with emerging data, and how limits in study design, sampling, and methodology limits study findings.

I want to bring special attention to the delirium and antipsychotics in palliative care review, as this study has given a lot of palliative care and intensivists pause regarding antipsychotics in their delirious patients. Looking at the article more closely, there are design, methodologic, and conclusion flaws that any psychiatrist can see as well as genuine concerns about these agents in the medically ill. However, we have very little literature about antipsychotics in delirium, let alone a RCT, and these results are very persuasive to our colleagues to abstain any antipsychotic usage. Dr. Silver's reflections, questions and points to the group should be required reading for us all to best critically evaluate the literature, be humble about we don't know, and also speak with expertise to our colleagues about what we do know.

Everolimus for treatment of tuberous sclerosis complex-associated neuropsychiatric disorders

Background and objectives: Tuberous sclerosis complex (TSC)is a genetic, neuro-cutaneous disorder frequently associated with psychiatric and neurological morbidity including intellectual disability, autism spectrum disorder, and other cognitive and behavioral problems (de Vries et al. 2015). A core deficit appears to be hyper-activation of the mechanistic target of rapamycin (mTOR) pathway. Inhibitors of mTOR have been effective in treatment of giant cell astrocytomas, renal angiomyolipomas, lymphangioleiomyomatosis, and epilepsy in patients with TSC. In animal models,

mTOR inhibitors have improved cognitive function and reduced behaviors consistent with autism leading to the hope that TSC associated neuropsychiatric disorders (TAND) might respond to mTOR inhibitors. The goal of this study was to test the safety of everolimus, an mTOR inhibitor, in children with TSC and to determine efficacy for treatment of TAND.

Methods: Participants were 6-21 years of age, had a verbal, performance, or full scale IQ > 60, and an established diagnosis of TSC. This was a two-site prospective, double-blind, placebo-controlled trial. Participants received everolimus 4.5 mg/m^2 or placebo daily for 6 months. Participants were monitored for adverse effects and assessed with standard measures of intelligence, learning, memory, attention, executive function, behavior, and academic skills.

Results: 52 patients were enrolled and 42 completed the study. Adverse events were mild to moderate with no difference in rate of adverse effects between drug and placebo. There was no difference between drug and placebo in 36/38 measures of cognition or behavior. One measure of executive function favored placebo and one measure of social cognition favored everolimus.

Conclusions/Commentary: Everolimus was safe but not effective for cognitive or behavioral function. Is it possible that the results would have been favorable if everolimus was started earlier? Everolimus has been used for children with TSC and refractory seizures as young as 2 years of age and for children with TSC and subependymal giant cell astrocytomas as young as 3 years of age. Adverse events were mild to moderate in both trials and, in the epilepsy trial, behavior and quality of life improved (Krueger et al. 2014; Franz et al. 2015).

Take-Away: Even with better understanding of the pathophysiological mechanisms of TSC, we still do not have a specific treatment for the cognitive and behavioral manifestations of TSC. We need to wait for additional trials before considering everolimus at an earlier age. Patients with TSC should receive a comprehensive assessment of cognition and behavior at diagnosis and reassessments at key points in development (Krueger DA, Northrup 2013).

References:

1. De Vries PJ, Whittemore VH, Leclezio L, et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND Checklist. Pediatr Neurol 2015; 52: 25-35.

2. Krueger DA, Wilfong AA, Holland-Bouley K, et alo. Everolimus treatment of refractory epilepsy in tuberosis sclerosis complex. Ann Neurol 2013; 74: 679-687.

3. Franz DN, Agricola K, Mays M, et al. Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. Ann Neurol 2015; 78: 929-938.

4. Krueger DA, Northrup H. International Tuberous Complex Consensus Group. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 255-265.

Reviewer: David W. Dunn, MD, Indiana University School of Medicine, Indianapolis IN

Source: Krueger DA, Sadhwani A, Byars AW, et al. Everolimus for treatment of tuberous sclerosis complex-associated neuropsychiatric disorders. Annals of Clinical and Translational Neurology. 2017; 4 (12): 877-887. Link here

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Hydrocortisone as an intervention for dexamethasone-induced adverse effects in pediatric patients with acute lymphoblastic leukemia: results of a double-blind, randomized controlled trial

Background: Corticosteroids, including dexamethasone, are integral to the treatment of leukemia in children. Neuropsychological adverse effects of these medications can significantly impact quality of life in ALL and potentially put patients in danger of physical harm. Previous studies have found benefit of anti-psychotics or benzodiazepines in mediating these effects, but these medications are not always effective and carry risk of potentially harmful side effects. The authors of this study cite recent research elucidating the pathophysiology of dexamethasone-related neuropsychological adverse effects. Specifically, that dexamethasone-induced cortisol depletion of the mineralocorticoid receptor in the brain may be the cause of these symptoms. They designed this double-blind, randomized controlled trial with a crossover design to test the utility of hydrocortisone as a treatment for some of the adverse neuropsychological and metabolic adverse effects of dexamethasone in pediatric leukemia patients.

Methods: Eligible patients were 3-16 years old, diagnosed with ALL, being treated on a medium-risk protocol (Dutch Childhood Oncology Group ALL-10 or ALL-11) that included 5-day dexamethasone pulses during the maintenance phase of treatment. The study interval included two sequential courses of dexamethasone and patients were randomly assigned to receive hydrocortisone during either the first or the second course of dexamethasone and placebo in the other. Hydrocortisone was dosed based on body surface area three times a day: 5, 3, and 2mg/meter squared. The primary outcome measure was the Strengths and Difficulties Questionnaire in Dutch (SDQ-Dut) which has 5 subscales: emotional symptoms, conduct problems, hyperactivity and inattention, peer relationship problems, and prosocial behavior. Patients were also monitored with questionnaires to track sleep, eating behavior, and physical activity, and completed neurocognitive tests on the first and last day of the steroid course. Physical monitoring included height, weight, waist-hip circumference, blood pressure, and blood work (lipid profiles, glucose, and insulin).

Results: There were no adverse effects that were attributable to hydrocortisone in either group. 46 patients completed the questionnaires at all 4 time points and 16 had a “clinically relevant” increase in psychosocial difficulties, which was defined as an increase of 5 in their SDQ-Dut total difficulties score. In these 16 patients, the authors found that hydrocortisone had an effect on the total difficulties score, bringing the score at the end of the dexamethasone course to within a normal range. Similarly, hydrocortisone did not improve sleep rating scores overall, but in the subset of patients who had

clinically relevant sleep disturbance with dexamethasone, the addition of hydrocortisone decreased the severity of this disturbance. Hydrocortisone did not have any effect on the physical parameters that they were monitoring.

Conclusion/Commentary: This study confirms past research that not all patients are equally impacted by adverse effects of corticosteroids. The findings suggest that those patients who are more affected may benefit from physiologic doses of hydrocortisone, a treatment without significant side effects. The fact that hydrocortisone did not improve metabolic adverse effects of hydrocortisone and suggest that these effects may have a different pathophysiology – an idea that could also inform further studies to help better understand the mechanism of the adverse effects of corticosteroids. The authors recommend further study focused on patients with symptoms related to dexamethasone to confirm effects of this intervention. However, the study did not include a discussion of the most severe neuropsychiatric effects – acute mania or psychosis – and when a trial of hydrocortisone could still be considered in these patients in addition to or instead of an antipsychotic. Finally, this study included only patients who were being treated on medium-risk protocols. Patients treated on high risk protocols receive more neurotoxic agents as well as higher and more frequent dosing of dexamethasone, so it is unclear if hydrocortisone would be useful in management of neuropsychiatric side effects in these patients.

Take-Away: Hydrocortisone seems to be a low-risk intervention that may alleviate some of the neuropsychiatric side effects of dexamethasone and could have the potential to improve quality of life in children and adolescents being treated for some types of leukemia. However, more studies are needed and it is unclear if there is a role for this medication in patients who develop severe neuropsychiatric side effects.

References:

1. Warris LT, van den Heuvel-Eibrink, MM, Aarsen FK, Pluijm SM, Bierings MB, can den Bos C, et al. Hydrocortisone as an Intervention for Dexamethasone-induced Adverse Effects in Pediatric Patients With Acute Lymphoblastic Leukemia: Results of a Double-Blind, Randomized Controlled Trial. J Clin Oncol 34:2287-2293, 2016.

Reviewer: Meredith MacGregor, MD, Memorial Sloan Kettering Cancer Center

Source: Hochhauser CJ, Lewis M, Kamen BA, et al: Steroid-induced alterations of mood and behavior in children during treatment for acute lymphoblastic leukemia. Support Care Cancer 13:967-74, 2005. Pubmed link

Parent and young adult satisfaction with psychiatry consultation services in a children's hospital

Background and Objective: Patient and family centered care is linked to improved health outcomes and promoting this model of care is felt to improve the overall quality of health care services. Patient satisfaction is an important way to evaluate the effectiveness of attempts at patient and family centered care. This study aimed to identify ways to enhance services provided by the inpatient child psychiatry consultation service and to guide development of future quality improvement projects. To achieve the project's goals the authors explored parent and young adult satisfaction with psychiatry consultation in a children's hospital.

Methods: The study was conducted at a 395 bed tertiary children's hospital where the Psychiatry Consultation Service (PCS) provides over 800 inpatient consultations a year on both general medical and surgical units. The team follows the principles outlined in the American Academy of Child and Adolescent Psychiatry's (AACAP) Practice Parameter for the Psychiatric Assessment and Management of Physically Ill Children and Adolescents. Due to lack of an appropriate measure, the PCS developed a Pediatric Psychiatry Consultation Satisfaction Survey (PPCSS) with 28 items, including two overall satisfaction measures along with four consultation components, used to evaluate effective psychiatric consultation in the pediatric setting. The study was conducted between June and August 2010; at the beginning of the consultation all parents and adult patients seen by the PCS on the general medical and surgical floors were informed that they might be asked to participate in a satisfaction survey after discharge. Exclusionary criteria were incomplete consultations, patients without parental involvement, and when deemed inappropriate by the consultant. Overall satisfaction was defined as the combination of overall helpfulness and whether the participant would recommend a psychiatric consultation to a friend.

Results: The PCS performed 122 consultations with 97 meeting inclusion criteria. Of those, eight (8%) declined, one (1%) participant's child passed away during admission, 27 (28%) did not complete the survey, and three (3%) parents/adult patients were missing current contact information. On average, those that did participate were younger than those participants that did not. No other significant differences were noted between participants and nonparticipants in terms of gender, race/ethnicity, length of stay, or any of the psychiatric diagnostic categories.

The helpfulness of the consultation was rated excellent/very good by 69% of participants (82% if good was included) with 88% saying they would recommend psychiatric consultation to a friend in need of services.

The level of satisfaction was significantly correlated with the consultants sharing clinical impression and recommendations ($p=0.018$), the communication and working relationship with the consultant ($p<0.001$), and the helpfulness of the consultant's interventions ($p<0.001$). The high level of satisfaction was not correlated with the consultants discipline (psychologist or psychiatrist), level of

training, psychiatric diagnosis given, person answering the survey, survey format, person initiating the consult, patient's medical diagnosis, or patient's demographic factors.

Conclusion/Take-Away: Consistent with the AACAP Practice Parameters (DeMaso et al), the authors found the most effective approach to psychiatric consultation with pediatric patients and families is "that of an empathic and active listening stance combined with both clear communication and a well delineated treatment plan that is integrated into a patient's overall care."

References:

1. Demaso, D.R., et al. Work Group on Quality Issues: American Academy of Child and Adolescent Psychiatry practice parameter for the psychiatric assessment and management of physically ill children and adolescents. J. Am Acad Child Adoles Psychiatry 2009; 48; 213-233
2. Lavakumar, M., et al. How Do You Know Your Consult Service is Doing a Good Job: Generating Performance Measures for C-L Service Effectiveness. Psychosomatics 2013 Nov-Dec; 54(6): 567-574.
3. Lavakumar, M., et al. Parameters of Consultee Satisfaction with Inpatient Academic Psychiatric Consultation Services: A Multicenter Study. Psychosomatics 2015 May-June; 56(3): 262-267

Reviewer: Kalonda Bradshaw, MD, The University of Texas Health Science Center at Houston

Source: Kitts, R., Gallager, K., Ibeziako, P., Bujoreanu S., Garcia, G., DeMaso, David. Parent and Young Adult Satisfaction with Psychiatry Consultation Services in a Children's Hospital. Psychosomatics 2013 Nov-Dec; 54(6): 575-584. Pubmed link

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Effect of dexmedetomidine added to standard care on ventilator-free time in patients with agitated delirium: a randomized clinical trial

Background: Delirium in hospitalized pediatric patients is an increasingly recognized, prevalent contributor to morbidity, mortality, length of intensive care stay, and duration of mechanical ventilation (Traube et al 2017), yet randomized controlled treatment studies in pediatric delirium have not been reported. The current adult study, from the Australian and New Zealand Intensive Care Society Clinical Trials Group, provides valuable data that could inform comparable RCT's in pediatric delirium patients and begin to transition to a more evidence-based footing.

Methods: The DahlIA (Dexmedetomidine to Lessen ICU Agitation) study randomly assigned 74 mechanically ventilated adults in whom extubation was delayed *exclusively due to inadequately controlled "agitation and delirium"*, either to dexmedetomidine (DEX) or placebo (PBO), in a multi-center, double-blind, parallel-group, placebo-controlled design. The authors underscore that "treating physicians had to feel that the degree of agitation itself, absent other factors, made taper of

sedatives, in preparation for extubation, unsafe..". At randomization, a mean (of drug and placebo recipients) of 95% of patients were receiving propofol, 21.5% either morphine or fentanyl, 21.5% an antipsychotic, and 13% midazolam.

Results: The primary outcome measure was the number of ventilation-free hours at 7 days post-randomization. Patients randomized to DEX had significantly more ventilator-free hours at 7 days (127.5) than in the PBO group (144.8), (*P*=.01). Median time to extubation also favored DEX vs. PBO: 21.9 vs. 44.3 hours (*P*<.001), bedside nurses judged their patients ready for extubation sooner (*P*<.001) and length of ICU stay was shorter in DEX than PCO (2.9 vs. 4.1 days) (*P*=.09). The authors conclude their findings support the use of DEX in patients with agitated delirium receiving mechanical ventilation in the ICU. They also speculate that DEX may have an inherent anti-delirium effect**.**

Conclusion/Commentary: This 2016 study, by what appears to be a highly reputable consortium of Australian and New Zealander adult intensivists, is the first to this reviewer's knowledge to report a blinded dexmedetomidine vs placebo trial addressing outcome measures highly relevant to those in pediatric psychosomatic medicine practice with delirious critically ill children: time off mechanical ventilation, duration of ICU stays, time to extubation, and bedside nurse time estimates on readiness for extubation. DEX outperformed placebo on every outcome measure, with statistical significance from the .01 to <.001 levels except for days of ICU stay (2.9 DEX vs 4.1 PBO), a qualitative but not statistically significant difference (*P*=.09). Further supporting the study's credibility is the use of accepted measures such as the CAM-ICU to measure delirium.

The authors interpret their findings as support for the use of DEX in patients with agitated delirium on mechanical ventilation. DEX, as a non-opioid, non-benzodiazepine, is unique among sedative agents commonly used both in adult and pediatric critical care settings in its specificity for the alpha-2-adrenergic receptor. Despite the lack of RCT's in pediatric populations, in the reviewer's experience, DEX is regularly being administered in PICU's for indications comparable to those in the Reade study, at Cleveland Clinic, Maine Medical Center, and Boston Children's, to name a few (Davis, S; Gunnoe, E, personal communications).

Take-Away: This study related adult studies, and the existing widespread empiric use of DEX in pediatric critical care settings make a compelling case for the planning of comparable studies in pediatrics. The regular and empiric use affords unique opportunities of further study and widespread dissemination at national meetings. DEX is effective, has a unique mechanism of action, and is less prone to adverse effects in the management of pediatric delirium. and has encouraging contributions to reducing morbidity, mortality, and patient suffering.

References:

1. Ely, EW; Pandharipande, PP. The Evolving Approach to Brain Dysfunction in Critically Ill Patients. *JAMA* 2016;315(14):1455-1456. doi:10.1001/jama.2016.2708
2. Traube, C; Silver, G. Iatrogenic Withdrawal Syndrome or Undiagnosed Delirium? Critical Care Medicine. June 2017; 45(6):e622-e623.

Reviewer: John P. Glazer, M.D., Boston Children's Hospital

Source: Reade MC, Eastwood GM, Bellomo R et al. Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients with Agitated Delirium A Randomized Clinical Trial. JAMA. 2016;315(14):1460-1468. Link

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Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in adult palliative care: A randomized clinical trial

Background and Objective: Delirium is highly prevalent in patients in palliative care (40%+ in adults presenting) and the symptoms can be quite distressing. Antipsychotics have been first line medications in the management of symptoms of delirium, but efficacy has not been established in placebo-controlled trials in palliative care. RCTs in critically ill patients have presented inconclusive findings of antipsychotics' benefit or harm in the setting of adult patients with delirium symptoms. This study intended to determine efficacy of risperidone or haloperidol relative to placebo for target delirium symptoms in this population.

Methods: Double-blind, parallel-arm, dose-titrated randomized clinical trial was conducted in 11 Australian hospice and hospital palliative care sites (part of National Palliative Care Program) Aug 2008-April 2014. 247 of 1819 patients were included with mean[SD]age, 74.9[9.8] years, 34% women, 88% with cancer, all with life limiting illness, delirium, diagnosed by DSM-IV criteria, MDAS score =/>7, and sum of Nursing Delirium Screening Scale (NuDESC) >/=1: behavioral, communication, and perceptual items. Excluded included 166-not interested, 449 non-delirious, 148-short life expectancy, and 750-other below.

Exclusion criteria: delirium due to substance withdrawal, neuroleptic malignant syndrome, regular use of antipsychotics, previous adverse reaction to antipsychotic drugs, extrapyramidal disorders, prolonged QT interval, clinicial predicted survival of </=7d, CVA or seizure in last 30days, pregnancy or breast feeding.
Required to speak English and swallow liquids. (57 excluded—27 did not meet criteria, 30 declined)
*Of those who participated, and who were included in the analysis:
82-Risperidone (31 discontinued: 16 deteriorated)
81-Haloperidol (18 discontinued: 8 deteriorated)
86-Placebo (15 discontinued: 7 deteriorated)

Interventions: Age adjusted titrated doses of oral risperidone, haloperidol, or placebo every 12hours for 72hours. Dosing: </= 65years: 0.5mg loading dose administered with the 1st dose of 0.5mg, then 0.5mg q12hours. Could be titrated to max dose 4mg/day. Dosing >65yrs doses were halved, and doses were increased if sum of NuDESC scores for items 2, 3, 4 was >/=1 for 48hrs.
Patients also received: supportive care, individualized treatment of precipitants, and **sub-cutaneous**

midazolam 2.5mg q2hours for severe distress or safety concerns if NuDESC score 2 and deemed to require immediate intervention. IV benztropine mesylate, 1-2mg was used for any EPS.

Results: There are no agreed upon outcome measures for relief of distressing delirium symptoms (nor clarity of benefit) nor agreed upon minimal differences in measurements of symptoms. Included in the intention to treat analysis: 82-risperidone, 81-haloperidol, 84-placebo. Average of the last 2 delirium symptom scores on day 3 were higher in treatment arms compared to placebo. EPS were higher in treatment arms. Improvement in mean group difference of delirium symptom score Day 0-Day 3. Placebo group had better overall survival than haloperidol (hazard ratio 1.73; 95%CI 1.2-2.50; P= .003) but not significantly different vs. risperidone (hazard ratio, 1.29; 95% CI, 0.91-1.84; P=.14).

Secondary outcomes:
Median survival for all participants in the placebo group was 26 days compared with 17 days for those in the risperidone arm and 16 days for those in the haloperidol arm.
In a post hoc analysis, those receiving an antipsychotic drug were approximately 1.5 times more likely to die (hazard ratio,1.47; 95% CI, 0.18-2.01; P = .01).
Midazolam use was significantly lower among those in the placebo arm compared with the risperidone and haloperidol arms combined on each study day (13 of 75 [17.3%] vs 50 of 144 [34.7%] on day 1; P = .007; 11 of 68 [16.8%] vs 40 of 121 [33.1%]
on day 2; P = .01; and 9 of 66 [13.6%] vs 32 of 108 [29.6%] on
day 3; P = .02). Of note: There were differences in opioid dosing in the 3 categories (e.g. higher in risperidone group). Benzodiazepines seemed to have been given only in the risperidone arm though interestingly midazolam was not considered an additional benzodiazepine in their secondary outcomes. EPS scores were higher in the antipsychotic arms but no serious events were noted. RASS scores were non-significantly lower in the antipsychotic arms.

Conclusion/Commentary: The authors concluded that patients receiving palliative care, supportive care, and individualized treatment of precipitants had resultant lower scores, and fewer distressing delirium symptoms than when haloperidol or risperidone were added. Also use of antipsychotics for delirium symptoms was associated with earlier death and greater use of rescue midazolam. Unfortunately, and fortunately, this study raises more questions than it does provide answers. Given the limitations of recognizing how to evaluate outcomes and meaning of delirium symptoms, it is unclear we can conclude the association with antipsychotic use and worse delirium symptoms, and also with premature death as resultant from antipsychotics or presenting differences in worse/worsening underlying severity of illness and/or presence of hypoactive delirium as evidenced by the lower RASS scores and possible sedation from the antipsychotic.

Take-Away:
This article raises a number of important concerns and research needs.

1. Identification of agreed upon outcome measures is needed. They use “distressing symptoms.” Studies looking at end of life in children and other psychological studies suggest that alert time spent with family allowing for good-byes and meaning-making may be more valuable than extra hours alive (Wiener 2010). How can we evaluate this?

2. Clarification of harm associated with delirium symptoms with benefit of reduction and how to measure these is needed.
3. The use oral antipsychotics may be associated with worse delirium symptoms in geriatric palliative care patients. The choice of high-EPS symptom burden oral antipsychotics is perplexing, limits the use in our sicker patients, and raises questions regarding the population selected and comparability to our pediatric population. This raises the question of the benefit of quetiapine vs. other antipsychotics especially in relation to helping to restore sleep wake cycle along with other sleep aids (eg. melatonin).
4. The use of oral antipsychotics may be associated with earlier death in geriatric palliative care patients.
5. Role of opiates is unclear.
6. This raises question for us in Pediatrics, may the use of antipsychotics cause more harm in our palliative care patients?
7. We need to better describe and evaluate what the needs of palliative care patients are and how to evaluate the use/harm of antipsychotics in this setting.

References: Wiener L, Ballard E, Brennan T, Battles H, Martinez P, and Pao M. How I Wish to be Remembered: The Use of an Advance Care Planning Document in Adolescent and Young Adult Populations. J Pall Med, September 2010. 11(10): 1309-1313. Published in Volume: 11 Issue 10: September 15, 2010

Reviewer: Gabrielle Silver, MD, Weil Cornell Medical College, NYC

Source: Agar, M. et al. Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium among patients in Palliative Care A randomized clinical trial. JAMA Internal Med 2017;177(1):34-42.doi:10.1001/jamainternmed.2016.7491. Published online December 5, 2016. Corrected on January 17, 2017. Link here

CLiPPs Feedback

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

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CLiPPs was created in 2015 and named at the AACAP Annual Conference during the Physically Ill Child Committee Meeting. *CLiPPs* thanks its reviewer team for their time and dedication educating colleagues.