JANUARY 2022 VOL X - ISSUE I

PEDIANEWS

The Official Newsletter of RxPups - Student Society of Pediatric Advocates

PediaNews Coordinator: Veli Uzunova | Pharm.D Candidate 2023

Editors

Linda Logan, Pharm.D, BCPS, BCPP, BCACP | Faculty Advisor

Aubrey Slaughter, Pharm.D | PGY-2 Pharmacy Resident

OUR MISSION

The Student Society of Pediatric Advocates is a student organization affiliated with the University of Georgia College of Pharmacy. We are a student group associated with the Pediatric Pharmacy Advocacy Group. The Mission of the SSPA is to bring awareness to the proper use of medication therapy in pediatric populations through various service and education- based initiatives. Service activities center around lending our medication- based knowledge to pediatric patients and their parents in our community. Educational activities are directed toward student members in an effort to safely and effectively extend pharmacy practice to pediatric populations by building relationships with mentors and professionals in the health care community, as well as supplementing didactic coursework with lectures by specialists and our peers. Overall, SSPA advocates for the safety and happiness of young patients while learning and having fun along the way. The purpose of our newsletter is to educate pharmacy students about pediatric pharmacy and advocate for pediatric patients within the University of Georgia College of Pharmacy.

2021-2022 EXECUTIVE BOARD

INSIDE THIS ISSUE

UNIVERSITY OF GEORGIA
College of Pharmacy

Antipsychotics Medications Alleviate Symptoms in Childhood Cancer

Written by Marwah Alzer, Pharm.D Candidate 2023

Children who are diagnosed with cancer not only struggle with the diagnosis but suffer from an array of negative emotions. Depressive disorders, anxiety, and stress-related symptoms are common among patients diagnosed with cancer. The prevalence of depression and anxiety in children with a cancer diagnosis ranges from 7-32%. [1] These symptoms can lead to an array of other issues such as nonadherence to a complicated regimen as well as a decrease in the quality of life. Many studies have looked at the use of antidepressants in children with cancer, but there is a lack of literature regarding the use of antipsychotics to alleviate these psychiatric symptoms. Antipsychotics are beneficial in aiding with sleep issues, irritability, nausea, and loss of appetite. With the reduced extrapyramidal side effects of second-generation antipsychotics, five second-generation antipsychotic agents have FDA-approved indications in for use in pediatrics five years or older: risperidone, aripiprazole, olanzapine, paliperidone, and quetiapine. [2]

At Schneider's Children Medical Center in Israel, a retrospective study was conducted to examine the benefit and tolerability of antipsychotics in children with cancer. The charts of children with a cancer diagnosis who had been examined by a psychiatrist and treated with an antipsychotic were reviewed. Patients treated with antipsychotic medications prior to initial psychiatric assessment without full documentation (full demographic information and two psychiatric assessments) before and after receiving the medication were excluded from the study. The patients included were diagnosed with psychiatric disorders using the Diagnostic and Statistical Manual of Mental Disorders-5 criteria.

Olanzapine and risperidone were the two most commonly used antipsychotics in this study. [3] The Clinical Global Impression-Severity (CGI-S) was used to correctly assess the symptomatic severity of the patient at the time of the referral. The Clinical Global Impression-Improvement (CGI-I) scale was used to examine the effects of each of the treatments. The final study groups consisted of 43 patients between 2-19 years of age. Of those 43 patients, 25 (58%) were treated with olanzapine while 18 (42%) were treated with risperidone. [4] The children treated in this study originally showed symptoms of depressed mood, irritability/agitation, and anxiety. Ninety percent (39) of the patients had medication-induced psychiatric disorders due to the usage of corticosteroids in their oncology treatment regimens.

After the initiation of the two antipsychotics, there was a decrease in CGI-S scores showing significant improvement in symptoms. Also, the CGI-I scores showed lower scores in the group receiving olanzapine therapy compared to those receiving risperidone. Seven patients (16%) in the group experienced mild side effects with olanzapine or risperidone and three of the seven (7%) patients discontinued treatment. [5]

The use of antipsychotics is evolving and becoming more prevalent. With an increased number of childhood cancer diagnoses, children are facing a myriad of psychological distress during their fight against cancer. This study supported that antipsychotic treatments may be appropriate in pediatric patients with depression when antipsychotic-target

TABLE 2. PREVALENCE OF PSYCHIATRIC-MEDICAL TARGET SYMPTOMS FOR TREATMENT WITH ANTIPSYCHOTICS IN PEDIATRIC ONCOLOGY AND BONE MARROW PATIENTS (N=43)

Symptoms	*Total* (n=*43*)	*Olanzapine* (n=*25*)	*Risperidone* (n=*18*)
Irritability/agitation	34 (79%)	18 (72%)	16 (89%)
Depressed mood	32 (74%)	21 (84%)	11 (61%)
Insomnia	27 (63%)	15 (60%)	12 (67%)
Anorexia	23 (53%)	15 (60%)	8 (44%)
Anxiety	22 (51%)	12 (48%)	10 (56%)
Nonadherence	13 (30%)	9 (36%)	4 (22%)
Suicidality	5 (12%)	2 (8%)	3 (17%)
Somatization	4 (9%)	2 (8%)	2 (11%)
Psychosis	3 (7%)	2 (8%)	1 (6%)
Hypomania/mania	1 (2%)	0	1 (6%)
Involuntary movements	0	0	0

comorbidities are present. These comorbidities included medication/medical condition-induced neuropsychic symptoms and medical indications such as nausea, sleeping disorders, and loss of appetite. Due to cancer patients having such complex healthcare needs, psychopathology tends to be underdiagnosed in this population. There is a need for a more active role of a physiatrist on the pediatric hematology oncology team.

The study also showed that there is an increase in the use of antipsychotics in adolescents for various indications. This may help foster an environment of acceptability for treating mental health conditions and prescribing antipsychotic medications. There has been an increase in knowledge and awareness in the United States to help treat a variety of symptoms with antipsychotics. [6] Children with cancer have seen an increase in comfort and quality of life after using the FDA approved antipsychotics.

References

1. Peled, Orit et al. “Psychopharmacology in the Pediatric Oncology and Bone Marrow Transplant Units: Antipsychotic Medications Palliate Symptoms in Children with Cancer.” Journal of child and adolescent psychopharmacology vol. 30,8 (2020): 486-494.
2. Harrison, Joyce Nolan et al. “Antipsychotic medication prescribing trends in children and adolescents.” Journal of pediatric health care: official publication of National Association of Pediatric Nurse Associates & Practitioners vol. 26,2 (2012): 139-45.
3. Peled, “Psychopharmacology in the Pediatric Oncology and Bone Marrow Transplant Units: Antipsychotic Medications Palliate Symptoms in Children with Cancer.”
4. Peled.
5. Peled, “Psychopharmacology in the Pediatric Oncology and Bone Marrow Transplant Units: Antipsychotic Medications Palliate Symptoms in Children with Cancer.”
6. Saljoughian, Manouchehr. “Atypical Antipsychotics: Safety and Use in Pediatric Patients.” US Pharmacist. 15 May 2015. https://www.uspharmacist.com/article/atypical-antipsychotics-safety-and-use-in-pediatric-patients.

New Treatment Options for Adolescents with Sickle Cell Disease

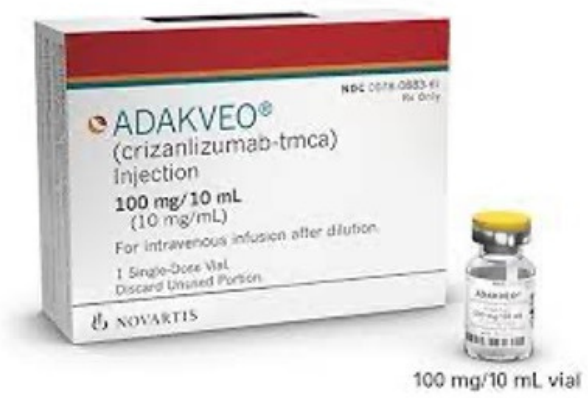
Written by Leslie Phillips, Pharm.D Candidate 2024

Sickle cell disease (SCD) is a genetic disorder that affects red blood cells. These blood cells become abnormal and sickled in shape resulting in decreased blood flow and oxygen distribution throughout the body. [1] The lack of oxygen-rich blood leads to many complications such as severe pain crises, acute chest syndrome, stroke, and organ damage. In 1972, the National Sickle Cell Disease Control Act was passed, and its purpose was to reduce morbidity and mortality of SCD, increase awareness through educating the public, and develop new modes of therapy. Since the act was passed, there has been a significant increase in research, treatment development, and education regarding SCD. [2]

Current treatment therapies for patients with SCD include penicillin prophylaxis, hydroxyurea, and blood transfusions. [3] A Penicillin Prophylaxis in Sickle Cell Disease Study (PROPS) found that the use of penicillin in children with SCD under 5 years of age significantly reduced severe bacterial infections. Because of the PROPS study, it is now recommended that children younger than 5 years of age with SCD receive 125 mg penicillin V potassium twice daily, and patients over the age of 5 years receive 250 mg twice daily. [4] Hydroxyurea was the first FDA-approved drug for sickle cell disease treatment. It works by increasing red blood cell hemoglobin F levels. As a result, blood cells stay round and are less likely to sickle. Studies have shown that hydroxyurea is clinically effective for the treatment of SCD in pediatric patients.

A study conducted in 2011 found that patients on hydroxyurea have an increase in hemoglobin levels and decrease hospitalization rates, which showed similar results as the landmark studies. The study further showed that when hydroxyurea is initiated in younger children (under the age of 5), there is an even greater reduction in hospitalizations. [5] Alongside hydroxyurea therapy, blood transfusions continue to be an imperative treatment option for SCD. Multiple studies have shown that when used together with hydroxyurea, primary and secondary strokes are prevented in children. Blood transfusions work by increasing hemoglobin and decreasing the amount of sickled hemoglobin leading to the prevention of vaso-occlusions, pain crises events, and other complications of the disease. One of the main drawbacks of blood transfusions is the risk of iron overload with chronic use. In fact, most patients require an iron chelation therapy after 1 year of blood transfusions. [6] New treatment options for sickle cell disease are continuously being studied. In fact, since 2017, the FDA has approved three new drug therapies for the treatment of SCD—Adakveo, Voxelotor, and Endari. [7]

Currently, a bone marrow transplant is the only approved therapy used to cure SCD. Current data shows promising results for transplantation in children under the age of 16. However, there are many risks involved with bone marrow transplants. New advances in gene therapy also show potential possibility for curing SCD. [3] The FDA approval of these three novel medicines adds more options to the developing repertoire of SCD treatment.



Endari (L-Glutamine)

Endari was approved by the FDA in July 2017 to treat SCD by reducing the acute complications in patients 5 years and older. Although the exact mechanism of action is unknown in sickle cell disease, it is thought to work by increasing the proportion of reduced nicotinamide adenine dinucleotide (NADH), and this leads to a reduction of oxidative stress resulting in fewer episodes of sickle cell related pain. The clinical trial found that there was a significant decrease in the number of pain crises among patients that received L-glutamine compared to those who received the placebo. There were also fewer hospitalizations among those receiving L-glutamine as well as fewer occurrences of acute chest syndrome compared to those receiving the placebo. [13]

Adakveo (Crizanlizumab)

Adakveo was first approved in November 2019 to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients, aged 16 years and older, with SCD.8 Adakveo is a P-selectin inhibitor that works by inhibiting the interactions between endothelial cells, platelets, red blood cells, and leukocytes. This results in decreased platelet aggregation, maintenance of blood flow, and an overall reduction of sickle-cell-related pain crises.9 A 2017 SUSTAIN study found patients who were given a high dose (5 mg/kg) of crizanlizumab saw an increased time between VOC events as well as a lower rate of uncomplicated crises per year compared to those in the placebo group. [10]

Oxbryta (Voxelotor)

Oxbryta was also approved by the FDA in November 2019 to treat SCD in patients 12 years and older. Oxbryta is unique from the other new medicines in that it directly addresses one of the root causes of SCD and its complications.11 It is a Hemoglobin S Polymerization Inhibitor that works by modulating hemoglobin's affinity to oxygen by binding and stabilizing hemoglobin S. As a result of the boosted hemoglobin affinity to oxygen, Oxbryta helps improve red blood cell deformability by decreasing sickling of red blood cells, increasing red blood cell half-life, and reducing anemia and hemolysis. The HOPE clinical trial found that when compared to a placebo group, patients that received Oxbryta saw a significant increase in hemoglobin levels as well as reduced markers of hemolysis. [12]

Table 1. A brief overview of three new FDA-approved drugs for the treatment of sickle cell disease. [9, 14, 15]

	Adakveo (Crizanlizuma)	Oxbryta (Voxelotor)	Endari (L-Glutamine)
FDA approval	November 2019	November 2019	July 2017
Age approved for	16 years and older	12 years and older	5 years and older
Pharmacologic category	Monoclonal Antibody	Hemoglobin S Polymerization Inhibitor	Amino Acid
Administration	Intravenous infusion over 30 minutes	Oral tablet	Oral powder
Dosing	5 mg/kg	1,500 mg	Weight-based: <30 kg = 5 g 30-65 kg = 10 g >85 kg = 15 g
Frequency	The initial dose is followed by a second dose at 2 weeks, and administered every 4 weeks	Once daily	Twice daily

References

1. National Heart, Lung, and Blood Institute. Sickle Cell Disease. September 01, 2020; https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease. Accessed October 22, 2021.
2. Manley, A F. "Legislation and funding for sickle cell services, 1972-1982." The American journal of pediatric hematology/oncology vol. 6,1 (1984): 67-71.
3. Ashorobi D, Bhatt R. Bone Marrow Transplantation In Sickle Cell Disease. [Updated 2021 Jul 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538515/
4. Cober, Mary Petrea, and Stephanie J Phelps. "Penicillin prophylaxis in children with sickle cell disease." The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG vol. 15,3 (2010): 152-9.
5. Quarmyne, Maa-Ohui, et al. "Hydroxyurea Effectiveness in Children and Adolescents with Sickle Cell Anemia: A Large Retrospective, Population-Based Cohort." American Journal of Hematology., vol. 92, no. 1, Wiley-Blackwell, 20171, pp. 77–81, doi:10.1002/ajh.24587.
6. Howard, Jo. "Sickle cell disease: when and how to transfuse." Hematology. American Society of Hematology. Education Program vol. 2016,1 (2016): 625-631. doi:10.1182/asheducation-2016.1.625
7. Ali, Muhammad Ashar et al. "Efficacy and safety of recently approved drugs for sickle cell disease: a review of clinical trials." Experimental hematology vol. 92 (2020): 11-18.e1. doi:10.1016/j.exphem.2020.08.008
8. Novartis. Adakveo. September 31, 2021; https://www.hcp.novartis.com/products/adakveo/sickle-cell-disease. Accessed October 22, 2021.
9. Lexicomp. Crizanlizumab (Lexi-Drugs). October 18, 2021; https://online.lexi.com/lco/action/doc/retrieve/adakveo. Accessed October 22, 2021
10. Ataga, Kenneth I., et al. "Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease." The New England Journal of Medicine., vol. 376, no. 5, Massachusetts Medical Society, pp. 429–39, doi:10.1056/NEJMoa1611770.
11. Thompson, Alexis. "A Targeted Agent for Sickle Cell Disease - Changing the Protein but Not the Gene." The New England Journal of Medicine., vol. 381, no. 6, Massachusetts Medical Society, pp. 579–80, doi:10.1056/NEJMe1906771.
12. Vichinsky, Elliott et al. "A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease." The New England journal of medicine vol. 381,6 (2019): 509-519. doi:10.1056/NEJMoa1903212
13. Niihara, Yutaka et al. "A Phase 3 Trial of l-Glutamine in Sickle Cell Disease." The New England journal of medicine vol. 379,3 (2018): 226-235. doi:10.1056/NEJMoa1715971
14. Lexicomp. Voxelotor (Lexi-Drugs). October 18, 2021. https://online.lexi.com/lco/action/doc/retrieve/voxelotor. Accessed October 22, 2021
15. Lexicomp. Glutamine (Lexi-Drugs). October 18, 2021. https://online.lexi.com/lco/action/doc/retrieve/endari. Accessed October 22, 2021

FDA Approves a New Autism Spectrum Disorder Diagnostic Aid

Written by Kara Phillips, Pharm.D Candidate 2024

According to the Centers for Disease Control and Prevention's (CDC) Autism and Developmental Disabilities Monitoring network, about 1 in 54 children are identified with autism spectrum disorder (ASD). The CDC identifies autism as a developmental disorder affecting cognitive, social, and behavioral skills, which requires an official diagnosis to begin suitable therapies. Developmental disorders such as ASD include a wide range of symptoms. The most common symptoms are minimal eye contact, slow verbal responses, intense interest in specific topics, repetitive behaviors, and adversity to change in routine. [3]

Until recently, diagnosing a child with ASD begins with a screen for developmental delays during typical wellness visits with a general pediatric practitioner. [1] More specifically, children are evaluated for autism spectrum disorders at both 18 and 24 months. [3] Children with low birthweight, premature birth, and older parents have an increased chance of having ASD and should be examined under higher scrutiny. [3] The Food and Drug Administration (FDA) states the average age of an ASD diagnosis is about 4.3 years. Children can be reliably diagnosed with ASD by the age of two; however, there is often a delay in diagnosis. The delay can occur because of the disorder's complexity and diversity in presentation or from a lack of prompt referrals to ASD specialists. [4]

To combat the delay in accurate diagnosis of pediatric developmental disorders, Cognoa, a behavioral health solutions company, created a new software to aid providers in assessing patients: the Cognoa ASD Diagnosis Aid, or Canvas Dx.

On June 2, 2021, the FDA authorized marketing of this new technology, with expectations for Canvas Dx to be available for provider use by the end of 2021. [5] Canvas Dx is indicated to assist in the diagnostic screening for ASD in children ages 18 months to 5 years old. [4] This diagnostic tool is only available by prescription and is to be used as an adjunct to the typical diagnostic process. [4] With shared clinical decision making, physicians can determine whether or not Canvas Dx is appropriate and prescribe accordingly.

The software consists of three main components: (1) a mobile app for a questionnaire and video submission, (2) video analysis by manufacturer-trained and certified specialists, and (3) an assigned health care provider portal to review answers and submissions. [1] A computer-based analysis is performed using a machine learning algorithm. After the information is processed digitally, one of three results will be reported: negative, positive, or inconclusive (insufficient data). [1] The trial conducted by Cognoa involved 425 children ages 18 months to 5 years old. [4] The conclusions of the software were directly compared to a panel of ASD expert providers. The device only reported conclusive results for 32% of the patients, and of these results, 81% of positive and 98% of negative results were confirmed by experts. [4]

As with any new screening technology, there are risks for inaccurate results. Canvas Dx had a false positive rate of 15 out of 303 children and a false negative rate of 1 out of 122 children.

These results do suggest that use of this technology can potentially delay correct diagnosis and subsequent therapies prescribed that could improve the child's outcome. [4] The recommendation for Canvas Dx to be used only as an adjunct to traditional processes is based on these limitations. Cognoa's website makes a strong statement in favor of such algorithms: "Machine learning can analyze large volumes of data much more quickly, analyzing hundreds of patient features and extrapolating thousands of data points in ways clinicians can't."

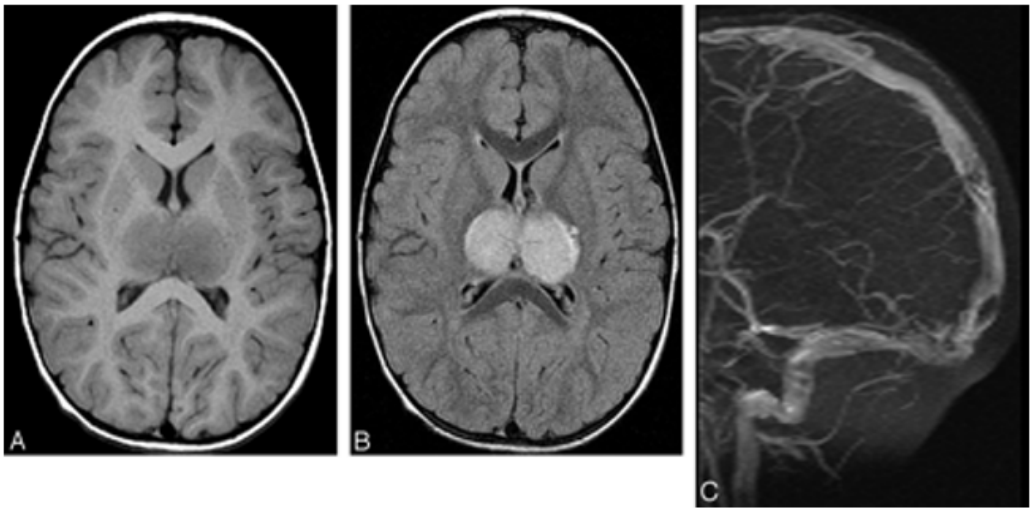
Technological advancements made by companies like Cognoa have the potential to change diagnostic processes. The complexity of ASD makes screening for such a wide range of symptoms difficult. Assistance from this software can be beneficial to the physicians and families involved by expediting the process to a conclusive diagnosis.

References

1. Abbas, H., Garberson, F., Liu-Mayo, S. et al. Multi-modular AI Approach to Streamline Autism Diagnosis in Young Children. Sci Rep 10, 5014 (2020). https://doi.org/10.1038/s41598-020-61213-w.
2. "Autism Spectrum Disorder (ASD)." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 19 Apr. 2021, www.cdc.gov/ncbddd/autism/index.html.
3. "Autism Spectrum Disorder." National Institute of Mental Health, U.S. Department of Health and Human Services, www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/.
4. "FDA Authorizes Marketing of Diagnostic Aid for Autism Spectrum Disorder." U.S. Food and Drug Administration, FDA, 2 June 2021, www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-diagnostic-aid-autism-spectrum-disorder.
5. "Leading the Way for Pediatric Behavioral Health." Cognoa, 7 June 2021, cognoa.com/.

Anticoagulation in Pediatric Cerebral Venous Thrombosis

Written by Gabrielle Bachner, Pharm.D Candidate 2022



http://www.ajnr.org/content/29/10/1961

Cerebral venous thrombosis (CVT) is a rare type of stroke that can be challenging to diagnose. In children, there is an incidence of 0.7 per 100,000 children per year, with a mortality of about 10%. CVT can be asymptomatic in some patients, but if symptoms become present, they may present as severe headache, visual disturbances, seizures, focal neurologic deficits, disturbances of consciousness, cognitive dysfunction, and death. Risk factors, specifically in pediatrics, can include use of hormonal contraceptives, trauma of the head or neck, traumatic head injury, thrombophilia, and cancer. Diagnosis is typically done through neuroimaging, which include a head computed tomography (CT), CT venography, magnetic resonance imaging (MRI), or MR venography. Sometimes multiple images will need to be obtained before a diagnosis of CVT is confirmed. Other tests ordered might include a complete blood count, chemistry panel, prothrombin time, activated partial thromboplastin time, and D-dimer, but none of these tests can confirm or deny a diagnosis.

Anticoagulation following a CVT is routine in the adult population, but there is limited data on the use of anticoagulants in the pediatric population following a CVT. The EINSTEIN-Jr trial looked at the use of rivaroxaban or traditional anticoagulation in children following a venous thromboembolism (VTE), which included patients with CVT among other VTE events. From this study, a subgroup analysis was done on the safety and efficacy of anticoagulants in the children who presented with CVT.

In this study, patients were started on 5 to 9 days of anticoagulation with unfractionated heparin, low-molecular-weight heparin (LMWH), or fondaparinux and from there separated into two groups to be on anticoagulation for 3 months following the CVT. One group was continued on standard anticoagulation and the other group was started on rivaroxaban. Standard anticoagulation included continuing heparin treatment or starting a vitamin K antagonist, like warfarin.

After a 3-month duration of anticoagulation, no patients experienced a recurrent venous thromboembolism. During the study, only 1 incidence of a major bleeding was reported, and this event occurred in the standard anticoagulation group. Five non-major, but clinically relevant, bleeding events occurred in the rivaroxaban group. There were no deaths reported in the study population during the trial. After consideration, it was seen to be both efficacious and safe to use anticoagulation in pediatrics after a CVT. While there was no statistical difference between the two study groups, there are some advantages with using rivaroxaban, specifically in pediatrics. Rivaroxaban is an oral medication, which is also available as a suspension, and does not require routine therapeutic drug monitoring, which requires multiple sticks in a child, which can be very uncomfortable.

Overall, initiation of anticoagulation for both treatment and prevention can be beneficial for the pediatric population with CVT. This is similar to the current treatment in the adult CVT population. More studies should be conducted on which anticoagulant to use, and the length of time for anticoagulation after the CVT. Hopefully, with this new information, more patients are started on anticoagulation, and it can prevent any recurrence for these patients.

References

1. Connor, Philip, et al. “Safety and Efficacy of Rivaroxaban in Pediatric Cerebral Venous Thrombosis (EINSTEIN-Jr CVT): For the EINSTEIN-Jr Cerebral Venous Thrombosis Trial Investigators.” Blood Advances, vol. 4, no. 24, Dec. 2020, pp. 6250–6258. EBSCOhost, doi:10.1182/bloodadvances.2020003244
2. Dlamini, Nomazulu et al. “Cerebral venous sinus (sinovenous) thrombosis in children.” Neurosurgery clinics of North America vol. 21,3 (2010): 511-27. doi:10.1016/j.nec.2010.03.006
3. Ferro, J., & Canhao, P. (2021, April 16). Cerebral venous thrombosis: Etiology, clinical features, and diagnosis. UpToDate. https://www.uptodate.com/contents/cerebral-venous-thrombosis-etiology-clinical-features-and-diagnosis?search=pediatric+cvt&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2.
4. Monagle, et al. “Bodyweight-Adjusted Rivaroxaban for Children with Venous Thromboembolism (EINSTEIN-Jr): Results from Three Multicentre, Single-Arm, Phase 2 Studies.” The Lancet., vol. 6, no. 10, Elsevier Ltd., doi:10.1016/S2352-3026(19)30161-9.

Impact of COVID-19 Pandemic on Children's Mental Health

Written by Sara Niazi, Pharm.D Candidate 2022

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus causing coronavirus disease 2019 (COVID-19), is continuing to have a drastic impact worldwide on nearly every aspect of people's lives, including their physical health, careers, and social lives. Although children apparently have a lower risk of developing the severe form of the COVID-19 disease and may require less hospital care and mechanical ventilation as compared to older individuals, that does not mean that children's physical and mental health are not at risk. In terms of their physical health, children are susceptible to developing a multisystemic inflammatory syndrome and are still at risk for contracting COVID-19. Regarding their mental health, which will be the focus of the remainder of this article, children are being affected by the disruption in normal daily routines due to social isolation and their inability to understand the short- and long-term consequences of this pandemic. Many studies have shown that how the pandemic affects mental health depends on variables that need to be considered and assessed. Some of these variables include: age; school closure; community and family relationships; screen time; along with risk factors and main concerns, including domestic violence, children with preexisting health conditions, children with COVID-19, and vulnerable socioeconomic conditions.

All age groups were seen to have more clinginess, irritability, and inattention in a children-specific study [21]. However, children aged 3-6 years old were more likely to manifest feelings of clinginess and fear that family members might contract the infection, whereas 6-18 year olds were more likely to show persistent inquiry and inattention. nother variable was gender, where studies with children and adolescents have shown that adolescent girls are more likely to present with depressive and anxiety symptoms. However, a study with children between 7-11 years old showed no differences in those subjects. School closure is a major variable that influences many aspects of children and adolescents' lives and behavior. Some have argued that schools are the primary source of consistent daily caloric intake in regard to children and adolescents' nutritional needs. Schools are also a source of physical activity along with structure and routine in children and adolescents' daily lives [3, 14, 20, 26, 30, 31, 32]. The interruption of these sources of normalcy is of concern to several authors analyzing the impact of this pandemic on children and adolescents' mental health [7, 18, 19, 28].Unfortunately, physical exercise was the lesser used technique among parents compared with media and reading entertainment to mitigate psychological problems during quarantine.

Family and community bonds and relationships play a critical role in mental health outcomes during the pandemic. For many, the presence of a supportive family can be protective against mental distress. However, an original study shows that adolescents left alone during workdays were more likely to show depression and anxiety [4]. Social relations were also seen to be relevant when associating mental health and quarantine motivation among younger people. Children who were social distancing because they prefer to stay home presented with less anxiety and depressive symptoms. However, young people who quarantined to avoid judgement or because they did not want to be infected with COVID-19 showed higher anxiety symptoms, while those who

quarantined because their friends told them to reported higher depressive symptoms. Due to obsessions and compulsions related to contamination, hoarding, and somatic preoccupation, they are expected to experience more distress. Another variable, more prevalent in many households, is the increase of screen time. Children and adolescents have been using technology for virtual learning due to the closing of schools. This same technology is also their source of social interaction and entertainment. On one hand, social media can be helpful for adolescents in protecting mental health by allowing access to information, identity development, social connection, and self-expression. On the other hand, there are also concerns about the increase in screen time due to its potentially harmful effects. Some concerns and risks include significant exposure to misinformation about COVID, disrupted sleep and circadian rhythms, and an increase in anxiety.

Reviewed literature states that children exposed to some risk factors are more vulnerable to developing mental health disorders during the COVID-19 pandemic [21]. Some specific groups identified were children with pre-existing health conditions and children living in vulnerable socioeconomic contexts. The risk factors mentioned in the literature included exposure to domestic violence or child maltreatment and infection by COVID-19 [21]. Some authors have argued that the in-home scenario brought on by the pandemic could result in children suffering or witnessing domestic violence or sexual abuse [6, 8, 9, 15, 31, 32]. Unfortunately, during quarantine, complaints may not be as frequent since there is no escape from perpetrators. Also, schools being closed exacerbates those issues since school is typically a safe place for children to report problems and where signs of abuse can be detected and reported. Children and adolescents with preexisting mental health disorders could be more susceptible to new mental health conditions and have specific needs that must be met. A single study found that history of chronic illness was associated with higher stress, anxiety, depression, and Post-Traumatic Stress Symptoms [29]. A concern related to mental health in children and adolescents is the risk of deterioration of their condition due to the pandemic. A lack of access to mental health services, regulations on travels, and quarantine may prevent patients from attending group interventions or from being able to get their medications. Therefore, it is crucial to ensure access to those services through telephone or online support and online pharmacies. It is still not certain how the pandemic will affect psychiatric disorders' features, including symptom severity, relapses, and intensity of mental healthcare [17]. Reviewed literature exemplifies mental health outcomes of the pandemic mainly with disorders including PTSD [3, 24, 27], eating disorders [11], Attention Deficit Hyperactivity Disorder (ADHD), and Autism Spectrum Condition (ASC) [2, 3, 7, 19, 32]. Those with PTSD may notice exacerbations of their symptoms in the new crisis scenario, while adolescents with eating disorders may be prevented from getting meal supervision and have their weight control affected. Additionally, children who have neurodevelopmental disorders, including ADHD and ASC might struggle with the lack of routine caused by the pandemic. One original study looked at children's ADHD behaviors during the COVID-19 outbreak and found those behaviors were worse compared with their normal state, showing increased irritability [21]. Unfortunately, children with Obsessive Compulsive Disorder (OCD) are suspected to be highly affected by this pandemic.

This is because cleanliness is a key protective measure against the spread of COVID-19, and according to United Nations'

policy guidelines to fight infection, one must be careful about washing his or her hands six times a day, and whenever he or she touches anything. The lockdown, which has made the healthy population distressed about possessing enough food, masks, and sanitizers has made it worse for those with hoarding disorder. Infection with COVID-19 also needs to be considered a risk factor for mental health disorder among children and adolescents because children face separation from their parents and caregivers when isolated. A Chinese paper reported feelings of insomnia and separation anxiety as the most common mental health problems reported by those children. The paper also recognizes the importance of screening for PTSD in patients who show symptoms, such as avoidance behaviors, nightmares, heightened reactions, etc. [10].

The pandemic may have a larger impact on the mental health of children and adolescents from lower socioeconomic conditions. Children from low-income families may rely only on school for healthy meals, mental health support, and physical exercise. Therefore, school closures and quarantine has prevented those children from accessing these services, which may lead to worsening mental health in these children. Along with those drawbacks, these children are also less likely to have proper access to the Internet or remote learning and interaction with their classmates and friends. The economic recession due to the pandemic may also lead to financial distress and unemployment for low-income families, which could increase chances of child maltreatment. According to expectations in literature, researchers have seen that adolescents of families with more significant financial difficulties are more likely to show higher depressive symptoms and lower feelings of belongingness [1]. Also, a study pointed out that in underprivileged families, in comparison to boys, girls have less access to gadgets, which may decrease their involvement in digital platforms of education. Due to this gender inequality, more girls are prone to bear the consequences of school dropouts once the lockdown is lifted [22].

Childhood and adolescence are critical developmental periods and special care must be taken to preserve and to promote their mental health. A study recently evaluated 1,036 quarantined children and adolescents in China from 6 to 15 years old, indicated that 112 of the children presented with depression, 196 with anxiety, and 68 with both [5]. A different study in India showed a high prevalence of psychological distress in quarantined children and adolescents due to the COVID-19 pandemic, including feelings of helplessness (66.11%), worry (68.59%) and fear (61.98%), as compared to children who were not quarantined [23]. Additionally, it was also shown in China that children and adolescents from 3–18 years had symptoms of inattention, clinging, worry and irritability during this pandemic [16].

Overall, there is a pressing need to plan longitudinal and developmental studies and implement an evidence-based plan of action to help meet the mental health needs of the children and adolescents during the pandemic as well as after the pandemic. It is necessary to ameliorate children and adolescents' access to support for mental health services, specifically towards providing ways to develop healthy coping mechanisms during the pandemic. Therefore, child and adolescent mental health policies with collaborative networks of healthcare practitioners, such as psychologists, psychiatrists, pediatricians, and volunteers are important.

References

1. Alvis L., Douglas R., Shook N.J., Oosterhoff B. 2020. Adolescents' Prosocial Experiences during the COVID-19 Pandemic: Associations with Mental Health and Community Attachments Lauren, PROSOCIAL BEHAVIOR and ADOLESCENT HEALTH.
2. Bandyopadhyay G., Meltzer A. Let's unite against COVID-19 - a New Zealand perspective. Ir. J. Psychol. Med. 2020 doi: 10.1017/ipm.2020.44.
3. Chatterjee S.S., Barikar C M., Mukherjee A. Impact of COVID-19 pandemic on pre-existing mental health problems. Asian Journal of Psychiatry. 2020;51:102071. doi: 10.1016/j.ajp.2020.102071.
4. Chen F., Zheng D., Liu J., Gong Y., Guan Z., Lou D. 2020. Depression and Anxiety Among Adolescents during COVID-19: A Cross-Sectional Study, Brain, Behavior, and Immunity.
5. Chen F., Zheng D., Liu J., Gong Y., Guan Z., Lou D. Depression and anxiety among adolescents during COVID-19: a cross-sectional study. Brain Behav Immun. 2020;88:36–38. doi: 10.1016/j.bbi.2020.05.061. S0889-1591(20)30891-6.
6. Clemens V., Deschamps P., Fegert J.M., Anagnostopoulos D., Bailey S., Doyle M., Eliez S., Hansen A.S., Hebebrand J., Hillegers M., Jacobs B., Karwautz A., Kiss E., Kotsis K., Kumperscak H.G., Pejovic-Milovancevic M., Christensen A.M.R., Raynaud J.-P., Westerinen H., Visnapuu-Bernadt P. Potential effects of "social" distancing measures and school lockdown on child and adolescent mental health. Eur. Child Adolesc. Psychiatr. 2020;29:739–742. doi: 10.1007/s00787-020-01549-w.
7. Cortese S., Asherson P., Sonuga-Barke E., Banaschewski T., Brandeis D., Buitelaar J., Coghill D., Daley D., Danckaerts M., Dittmann R.W., Doepfner M., Ferrin M., Hollis C., Holtmann M., Konofal E., Lecendreux M., Santosh P., Rothenberger A., Soutullo C., Steinhausen H.C., Taylor E., van der Oord S., Wong I., Zuddas A., Simonoff E. ADHD management during the COVID-19 pandemic: guidance from the European ADHD Guidelines Group. The Lancet Child and Adolescent Health. 2020;4642:412–414. doi: 10.1016/S2352-4642(20)30110-3.
8. Crawley E., Loades M., Feder G., Logan S., Redwood S., Macleod J. Wider collateral damage to children in the UK because of the social distancing measures designed to reduce the impact of COVID-19 in adults. BMJ Paediatrics Open. 2020;4 doi: 10.1136/bmjpo-2020-000701.
9. Cuartas J. Heightened risk of child maltreatment amid the COVID-19 pandemic can exacerbate mental health problems for the next generation. Psychological Trauma: Theory, Research, Practice, and Policy. 2020 doi: 10.1037/tra0000597.
10. Cui Y., Li Y., Zheng Y. Mental health services for children in China during the COVID-19 pandemic: results of an expert-based national survey among child and adolescent psychiatric hospitals. Eur. Child Adolesc. Psychiatr. 2020;29:743–748. doi: 10.1007/s00787-020-01548-x.
11. Davis C., Ng K.C., Oh J.Y., Baeg A., Rajasegaran K., Chew C.S.E. Caring for children and adolescents with eating disorders in the current coronavirus 19 pandemic: a Singapore perspective. J. Adolesc. Health. 2020;67:131–134. doi: 10.1016/j.jadohealth.2020.03.037.
12. de Figueiredo CS, Sandre PC, Portugal LCL, Mázala-de-Oliveira T, da Silva Chagas L, Raony Í, Ferreira ES, Giestal-de-Araujo E, Dos Santos AA, Bomfim PO. COVID-19 pandemic impact on children and adolescents' mental health: Biological, environmental, and social factors. Prog Neuropsychopharmacol Biol Psychiatry. 2021 Mar 2;106:110171. doi: 10.1016/j.pnpbp.2020.110171. Epub 2020 Nov 11. PMID: 33186638; PMCID: PMC7657035.
13. Fegert JM, Vitiello B, Plener PL, Clemens V. Challenges and burden of the Coronavirus 2019 (COVID-19) pandemic for child and adolescent mental health: a narrative review to highlight clinical and research needs in the acute phase and the long return to normality. Child Adolesc Psychiatry Ment Health. 2020 May 12;14:20. doi: 10.1186/s13034-020-00329-3. PMID: 32419840; PMCID: PMC7216870.
14. Golberstein E., Wen H., Miller B.F. Coronavirus disease 2019 (COVID-19) and mental health for children and adolescents. JAMA Pediatrics. 2020 doi: 10.1001/jamapediatrics.2020.1456
15. Green P. Risks to children and young people during covid-19 pandemic. BMJ. 2020;369:m1669. doi: 10.1136/bmj.m1669.
16. Jiao W.Y., Wang L.N., Liu J., Fang S.F., Jiao F.Y., Pettoello-Mantovani M., Somekh E. 2020. Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic. 264–266.
17. Kaufman K.R., Petkova E., Bhui K.S., Schulze T.G. A global needs assessment in times of a global crisis: world psychiatry response to the COVID-19 pandemic. BJPsych Open. 2020;6 doi: 10.1192/bjo.2020.25.
18. Lambrese J.v. Helping children cope with the COVID-19 pandemic. Cleve. Clin. J. Med. 2020:13. doi: 10.3949/ccjm.87a.ccc010.
19. Lee J. Mental health effects of school closures during COVID-19. The Lancet Child & Adolescent Health. 2020;4:421. doi: 10.1016/S2352-4642(20)301097.
20. Liu J.J., Bao Y., Huang X., Shi J., Lu L. Mental health considerations for children quarantined because of COVID-19. The Lancet Child & Adolescent Health. 2020;4:347–349. doi: 10.1016/S2352-4642(20)30096-1.
21. Marques de Miranda D, da Silva Athanasio B, Sena Oliveira AC, Simoes-E-Silva AC. How is COVID-19 pandemic impacting mental health of children and adolescents?. Int J Disaster Risk Reduct. 2020;51:101845. doi:10.1016/j.ijdrr.2020.101845
22. McQuillan H., Neill B.O. Gender differences in children's internet use: key findings from Europe. J. Child. Media. 2009;3(4):366–378. doi: 10.1080/17482790903233408.
23. Saurabh K., Ranjan S. Compliance and psychological impact of quarantine in children and adolescents due to Covid-19 pandemic. Indian J. Pediatr. 2020;87(7):532–536. doi: 10.1007/s12098-020-03347-3.
24. Sharma V., Reina Ortiz M., Sharma N. Risk and protective factors for adolescent and young adult mental health within the context of COVID-19: a perspective from Nepal. J. Adolesc. Health. 2020;67:135–137. doi: 10.1016/j.jadohealth.2020.04.006.
25. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. Psychiatry Res. 2020;293:113429. doi:10.1016/j.psychres.2020.113429
26. Thakur K., Kumar N., Sharma N. Effect of the pandemic and lockdown on mental health of children. Indian J. Pediatr. 2020 doi: 10.1007/s12098-020-03308-w.
27. Tracy M., Norris F.H., Galea S. Differences in the determinants of posttraumatic stress disorder and depression after a mass traumatic event. Depress. Anxiety. 2011;28:666–675. doi: 10.1002/da.20838.
28. Vanderloo L.M., Carsley S., Aglipay M., Cost K.T., Maguire J., Birken C.S. Applying harm reduction principles to address screen time in young children amidst the COVID-19 pandemic. J. Dev. Behav. Pediatr. 2020;41:335–336. doi: 10.1097/dbp.0000000000000825.
29. Wang C., Pan R., Wan X., Tan Y., Xu L., Ho C.S., Ho R.C. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int. J. Environ. Res. Publ. Health. 2020;17:1729. doi: 10.3390/ijerph17051729.
30. Wang G., Zhang Y., Zhao J., Zhang J., Jiang F. Mitigate the effects of home confinement on children during the COVID-19 outbreak. Lancet. 2020;395:945–947. doi: 10.1016/S0140-6736(20)30547-X.
31. Witt A., Ordóñez A., Martin A., Vitiello B., Fegert J.M. Child and adolescent mental health service provision and research during the Covid-19 pandemic: challenges, opportunities, and a call for submissions. Child Adolesc. Psychiatr. Ment. Health. 2020;14:19. doi: 10.1186/s13034-020-00324-8.
32. Wright B., Spikins P., Pearson H. Should autism Spectrum conditions Be characterised in a more positive way in our modern world? Medicina. 2020;56:233. doi: 10.3390/medicina56050233.