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PANDAS/PANS Legislation
Evidence-Based Response to Common Oppositional Arguments

Common Oppositional Claims	Evidence-Based Response
The following statement is inaccurate. "It takes decision making out of the hands of medical providers".	Just the opposite. A 2017 American Medical Association survey of 1,000 physicians found that 84% of those surveyed felt the burdens imposed by insurers to obtain care were high/extremely high and 92% surveyed indicated that these barriers can have a **negative impact on patient's outcomes.** PANDAS/PANS legislation removes these barriers **allowing the physician to determine the most clinically appropriate treatment for their patient**. In the words of a Northwest pediatrician, 'The lack of insurance coverage absolutely impacts my prescribing practices for children with PANDAS/PANS'.
The following statement is inaccurate. All of the 870+ children in Alaska affected by these disorders will require IVIG and/or Plasmapheresis.	It is estimated that only a small sub-set, those with moderate-severe severity, will require IVIG and/or Plasmapheresis. According to the 2017 Journal Child and Adolescent Pharmacology guidelines, "A small but significant subset, estimated to be 10-15% of referred children, fail to improve with these conventional measures and require immunomodulatory therapy with intravenous immunoglobulin (IVIG), therapeutic plasmapheresis (also known as plasma-exchange), or other modalities". The National Institute of Mental Health confirms this small subset as well indicating that immunotherapies are reserved for the sickest children. The correct estimate of those who would need immunotherapy in Alaska would be between 131-174 children and that is assuming every child with PANDAS/PANS has been diagnosed accurately in our state.
The following statement is inaccurate. IVIG and plasmapheresis, are NOT evidence-based treatments for PANDAS/PANS and should be considered experimental and/or investigational.	IVIG has been used for over 70 years and has well established anti-inflammatory and immunomodulatory properties (Annals of American Thoracic Society). The efficacy of immunomodulatory treatment in PANDAS/PANS has been rigorously examined since 2015. Recent evidence overwhelmingly supports inclusion of IVIG in the levels of treatment available for children with PANDAS and PANS. Based on extensive systematic reviews from several specialty areas, treatment studies, and the national consensus guidelines of the PANS Research Consortium and PANDAS Physician Network, "IVIG is indicated for the treatment of a small but significant subset of children who meet the criteria." The American Society for Apheresis (ASFA) included PANDAS in its guidelines published in the Journal of Clinical Apheresis (JCA) in its last two editions. 'In severely symptomatic patients with PANDAS or SC, immunomodulatory therapies, such as IVIG...or TPE, have been shown to be effective in reducing symptom severity or shorten the course.'" As you will see by the medical efficacy update and studies linked below, IVIG is the gold standard of care for a specific severity of P/P children and has been researched extensively. PANDAS Medical Efficacy Update by Dr. Sue Swedo (NIMH Emerita) and Dr. Mark Pasternack of Harvard can be found in uploaded written testimonies for HB 2390. Published research findings over the last two years: • Yale Study Finds Antibodies in PANDAS • Th17 Lymphocytes Drive Vascular and Neuronal Deficits in a Mouse Model of Postinfectious Autoimmune Encephalitis • Treatment of Pediatric Acute-Onset Neuropsychiatric Disorder in a Large Survey Population • Benefits of IVIG in Pediatric Acute-Onset Neuropsychiatric Syndrome

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	• Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue • Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus Immunology • Treatment of PANDAS and PANS: a systematic review • Clinical-Serological Characterization and Treatment Outcome of a Large Cohort of Italian Children with Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infection and Pediatric Acute Neuropsychiatric Syndrome A 2018 review published in the official journal of the European Paediatric Neurology Society...classified IVIG as a first line therapy in the treatment of PANDAS. '...there are general themes that broadly apply including: early diagnosis and treatment is better, minimize the severity of disease, escalate treatment if the patient is not responding to initial treatments, and minimize relapse.' ASFA American Society for Apheresis · EUROPEAN PAEDIATRIC NEUROLOGY SOCIETY · AAAAI American Academy of Allergy Asthma & Immunology
The following statement is inaccurate. There is not consensus on diagnostic and treatment guidelines, including the use of immunotherapies.	In 2017, the PANS Research Consortium (PRC) published a guideline series in four parts with contributing experts from more than two dozen academic institutions across the United States. Researchers and clinicians from the National Institute of Mental Health (NIMH), Harvard, Yale, Georgetown, Columbia, Stanford and other academic institutions pooled their data and clinical experience with more than 1000 PANDAS and PANS patients to develop best practice recommendations. These can be summarized as: Treat the SYMPTOMS, remove the SOURCE, and modulate the IMMUNE SYSTEM to reduce neuroinflammation. In December of 2020, PANDAS Physician Network, national expert body, released updated diagnostic and treatment guidelines further clarifying diagnostic and treatment guidelines via clinical algorithm. JCAP 2017 Guidelines for treating PANS/PANDAS Please also see: • PANDAS Medical Efficacy Update • PANDAS Physicians Network • Massachusetts Child Psychiatry Access Program (MCPAP) MCPAP Massachusetts Child Psychiatry Access Program · PANDAS PHYSICIANS NETWORK PPN A DIVISION OF THE FOUNDATION FOR BRAIN SCIENCE AND IMMUNOLOGY
The following statement is inaccurate. The National Institute of Mental Health (NIMH) does not recognize PANDAS/PANS and does not support IVIG and Plasmapheresis.	The original research regarding PANDAS/PANS originated in the NIMH with Dr. Sue Swedo's revelation that strep caused OCD. Dr. Sue Swedo is now recognized as a NIMH Emerita. This legislation provides access to immune treatment in a manner consistent with NIMH recommendations:

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	NIMH website: What about treating PANDAS with plasma exchange or immunoglobulin (IVIG)?: "Plasma exchange or immunoglobulin (IVIG) may be a consideration for acutely and severely affected children with PANDAS. Research suggests that both active treatments can improve global functioning, depression, emotional ups and downs, and obsessive-compulsive symptoms. [Given side effects and risk of infection,] the treatments should be reserved for severely ill patients and administered by a qualified team of healthcare professionals." Further, the Massachusetts Child Psychiatry Access Program (MCPAP), which is funded by the Department of Mental Health, substantiates these guidelines: Massachusetts Child Psychiatry Access Program (MCPAP) NEWS: Clinical Conversation: November 20, 2018 "Immune therapies – used when there is clear evidence of neuroinflammation or postinfectious autoimmunity...In moderate to severe cases, intravenous immunoglobulin (IVIG) may be used."
The following statement is inaccurate. There is not sufficient research and/or the published research that exists is too limited, without control groups.	As stated above, IVIG has been rigorously examined since 2015. Recent evidence overwhelmingly supports inclusion of IVIG in the levels of treatment available for children with PANDAS and PANS and is agreed upon by a national body of medical experts and given as a treatment option listed by the NIMH. Randomized clinical trials are not always feasible in every population, especially in vulnerable populations. The very sickest patients (and their parents) may not consent to a trial with a placebo just because the risk of not getting potential treatment is too high. There is controversy even amongst researchers when it comes to the inclusion of pediatric subjects in clinical trials because of their inability to consent for themselves and when receival of a placebo could delay much needed treatment for a child who is already severely ill. Please refer to studies referenced above.
The following statement is inaccurate. Insurance mandates add to the cost of healthcare for plan members, insurers and the state.	Massachusetts did a cost analysis in 2015, updated in 2019, that reflected the negligible cost impact to plan members which is highlighted in the 2015 CHIA report, and summarized in the PANDAS Medical Efficacy Update. "Given the narrow subset of patients requiring IVIG (an estimated 10-15%) ...coverage of treatment would result in a slight increase in premiums for insurance holders in the Commonwealth of Massachusetts. According to the report, 'requiring coverage for this benefit by fully insured health plans would result in an **average annual increase, over five years, to the typical member's monthly health insurance premiums of between $0.003 (0.001%) and $0.039 (0.008%) per year**.'" The upstream cost of not treating the most severely affected PANDAS/PANS children in our state could result in costs related to lifetime mental illness, social security disability, education costs (504s, IEPs, 1:1 tutors, special education), Medicaid enrollment, psychiatric residency and hospitalization, homelessness, and suicide. The lifetime burden of serious mental illness estimated to be 1.84 million per patient.
The following statement is inaccurate. There isn't an ICD code for PANDAS/PANS	Effective 10/1/2020, ICD 10 has assigned a corresponding code for PANDAS which is 89.89 (Other specified disorders involving the immune mechanism, not elsewhere classified), and the new version of the ICD-11 will include a specific code for PANDAS (8E4A.0 Paraneoplastic or autoimmune disorders of the central nervous system, brain or spinal cord). ICD codes are developed by the World Health Organization and maintained by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC).

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The following statement is inaccurate. IVIG and PE is invasive and expensive.	According to the Hospital for Sick Kids, IVIG is a safe treatment for children. Most side effects (headache, nausea, dizziness) are mild and easy to control. The process of administering is as simple as placing a hollow needle into a vein in your child's hand or arm to infuse healthy antibodies. According to the UT Southwestern Medical Center, "plasma exchange is a safe procedure with a few side effects". The total cost of IVIG therapy ranges from $5000 to $20,000, depending on the patient's weight. The private pay cost of these therapies is cost prohibitive for most Alaska families however, the cost to insurers is much lower due to contracted rates and their practice of passing costs on to their plan members. Despite this practice, a 2015 Massachusetts financial analysis of member impact by the inclusion of IVIG treatment resulted in less than pennies a month even at the highest utilization (20%). Meanwhile Alaska insurers post revenue and profitability in the multi-millions.

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Senator James Welch, Co-Chairman of the Joint Committee on Financial Services
Room 413
24 Beacon Street
Boston, MA 02133

Representative James Murphy, Co-Chairman of the Joint Committee on Financial Services
Room 254
24 Beacon Street
Boston, MA 02133

Dear Senator Welch and Representative Murphy:

On behalf of my colleagues I am forwarding an updated supplemental analysis for the 2015 CHIA report regarding An Act Relative to Insurance Coverage for PANDAS/PANS (H.920/S.613). This was requested by Adam Horgan and Lisa Pellegrini, legislative research staff members for the Joint Committee on Financial Services at the time of our discussions on PANDAS Awareness Day, October 10, 2019.

Thank you for your continued consideration.

Sincerely,

Mark S. Pasternack MD.

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MEDICAL EFFICACY UPDATE:
AN ACT RELATIVE TO INSURANCE COVERAGE FOR PANDAS/PANS (H.920/S.613)

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HISTORY OF THE BILL

An Act Relative to Insurance Coverage for PANDAS/PANS (H.920/S.613) provides for insurance coverage of physician-recommended therapies, including intravenous immunoglobulin therapy (IVIG), for children suffering from Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus (PANDAS) and Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS).[1] Passage of this bill would give physicians access to higher level treatment options for their most ill PANDAS and PANS patients. According to an actuarial assessment conducted by the Center for Health Information Analysis (CHIA) of the Commonwealth of Massachusetts in 2015, coverage would have a minimal impact on premiums.[2,3] Recent literature, published in the four years following the initial CHIA report, recommends IVIG to treat a subset of patients with PANDAS and PANS and supports its efficacy. The present update summarizes these peer-reviewed studies, reviews, and international treatment guidelines.

PANDAS AND PANS

- PANS is a collection of disorders characterized by the abrupt onset of obsessive-compulsive disorder (OCD) or eating restrictions and a variety of cognitive, behavioral, neurological and somatic symptoms and signs. In most cases, neuroinflammation has been found to be the cause of the neuropsychiatric symptomatology.

- When PANS is triggered by prolonged infection with, or exposure to group A streptococcal (GAS) bacteria, it is known as PANDAS, or in severe cases, autoimmune encephalitis of the basal ganglia. Antigens on the strep bacteria's cell wall provoke the production of antibodies which cross-react with brain tissue, leading to neuroinflammation and the complex symptoms of PANDAS.

- PANDAS and PANS are most commonly recognized by the unusually abrupt and dramatic symptom onset. In addition to the primary symptoms of OCD or eating restrictions, children may experience personality changes, extreme emotional lability, severe separation anxiety, and neurologic signs, such as sensory abnormalities, motor and/or vocal tics, and cognitive changes. Other common symptoms include behavioral (developmental) regression, physical aggression, sleep difficulties, urinary frequency/enuresis, and a number of additional debilitating symptoms such as hallucinations and delusions.

- The diagnosis of PANDAS can be challenging because inciting streptococcal infections may be subclinical ("silent") and suspected only after the abrupt onset of this dramatic clinical picture. Although elevated GAS antibody tests are classically observed with immunologic complications of streptococcal infection, it is now recognized that these tests may be falsely negative rather frequently.[4] Thus, the recognition of the clinical features of PANDAS and the response to appropriate therapy are important in the clinical management of these children despite limitations in laboratory assessment.

SUMMARY OF TREATMENT

In 2017, the PANS Research Consortium (PRC) published a guideline series in four parts with contributing experts from more than two dozen academic institutions across the United States.[5,6,7,8] Researchers and clinicians from the National Institute of Mental Health (NIMH), Harvard, Yale, Georgetown, Columbia, Stanford and other academic institutions pooled their data and clinical experience with more than 1000

PANDAS and PANS patients to develop best practice recommendations. These can be summarized as: Treat the SYMPTOMS, remove the SOURCE, and modulate the IMMUNE SYSTEM to reduce neuroinflammation.[5]

Mild to moderate cases of PANDAS and PANS are often managed successfully with antibiotic and nonsteroidal anti-inflammatory therapy. More severely afflicted children frequently require prednisone and psychotropic medications. A small but significant subset, estimated to be 10-15% of referred children, fail to improve with these conventional measures and require immunomodulatory therapy with intravenous immunoglobulin (IVIG), therapeutic plasmapheresis (also known as plasma-exchange), or other modalities.[7]

CURRENT COVERAGE

Despite support of IVIG for severe cases of PANDAS and PANS in published studies and reviews and the PANS Research Consortium consensus, few insurers have recognized these recommendations and incorporated them into their policies. Tufts added coverage of IVIG for treatment of PANDAS for their Health Freedom plans on September 10, 2019.[9] Families have also accessed treatment through MassHealth, which includes IVIG therapy in their covered services for PANDAS and PANS. In their documentation, MassHealth has designated IVIG as medically necessary when approving it for these children.

Between 2017 and 2019, Illinois, Minnesota, Arkansas, Delaware, and New Hampshire adopted legislation requiring insurance coverage for immunomodulating therapies, including IVIG, for PANDAS and PANS. Ten additional states have legislation pending or in development.

COST OF IMPLEMENTING THE BILL

Given the narrow subset of patients requiring IVIG calculated by the 2015 CHIA report, coverage of treatment would result in a slight increase in premiums for insurance holders in the Commonwealth of Massachusetts. According to the report, "requiring coverage for this benefit by fully-insured health plans would result in an average annual increase, over five years, to the typical member's monthly health insurance premiums of between $0.003 (0.001%) and $0.039 (0.008%) per year."[2] We ask for this cost to be considered in contrast to the enormous financial burden on patients with PANDAS and PANS, their families, communities, and insurers when effective treatment is delayed or unavailable.

MEDICAL EFFICACY: AN UPDATE BASED ON EMPIRICAL EVIDENCE

In the four years following the 2015 CHIA Report, consensus guidelines, systematic reviews, and IVIG treatment studies were published representing experts in psychiatry, infectious disease, general pediatrics, immunology, rheumatology, neurology, neuroimmunology, and basic science. The PANS Research Consortium immunomodulatory task force included recommendations for IVIG therapy for patients with PANDAS and PANS in their 2017 consensus guidelines.[7]

> The authors believe that PANS patients presenting with severe symptoms and a chronic-static or chronic-progressive course require consideration of more intensive immunomodulatory approaches like those used for neuropsychiatric systemic lupus erythematosus (NPSLE), central nervous system (CNS) vasculitis, autoimmune encephalitis (AE), chronic-progressive MS, chronic-progressive Behçet's disease, and other persistent neuroinflammatory disorders.[7]

These guidelines further described the rationale for immunomodulatory therapy, including IVIG, in the treatment of PANDAS and PANS, in the context of its well-described predecessor and model, Sydenham chorea (SC).[7]

> Accumulating evidence supports conceptualizing PANS as an immune-mediated brain disease, akin to SC and PANDAS, involving the caudate, putamen, and other basal ganglia structures. Data supporting this model come from epidemiological, clinical, paraclinical, translational, and basic science investigations of PANDAS and SC.[7]

Several literature reviews categorized PANDAS and PANS with pediatric neurological, neurodevelop-mental, and neurodegenerative disorders in their determination of the medical efficacy of treatment with IVIG. A 2016 review acknowledged the wide use of IVIG despite the challenges and limitations of research in children with neurological and neurodevelopmental conditions such as PANDAS, SC, autoimmune encephalitis (AE), Myasthenia gravis, and Guillain-Barré syndrome (GBS). Their systematic analysis of data from previous studies supported IVIG treatment for many disorders, including PANDAS.[10]

> We conclude that it is likely that IVIG improves recovery in selected patients with paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (level 2). We recommend that IVIG should be considered in selected patients with a diagnosis of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (grade B).[10]

Another systematic literature review determined that IVIG was effective in PANDAS and other neurodegenerative conditions including SC, Tourette's syndrome (TS), Multiple Sclerosis (MS), and acute disseminated encephalomyelitis (ADEM).[11] "In the studies we analyzed, IVIG was (sic) found to be efficient in the treatment of post-streptococcal neurodegenerative disorders, even if in PANDAS, plasma-exchange (PE) showed a higher efficiency."[11]

In the American Academy of Allergy, Asthma, and Immunology's 2017 Work Group Report, the authors conducted a rigorous review of literature prior to June, 2015, that referenced immunoglobulin therapy for an exhaustive list of conditions, including primary and secondary immunodeficiency as well as autoimmune, atopic, infection-related, and neurologic diseases.[12] According to the report, IVIG is a treatment recognized for anti-inflammatory, immunomodulatory, and infection-fighting capabilities. Taking into account factors such as benefit versus risk, finite supply, and often limited research, their analysis determined whether IVIG would provide benefit for each diagnosis. Regarding PANDAS, the authors concluded, "immune-based therapies should be used only in cases in which it is clear that the neuropsychiatric symptoms are related to an autoimmune response, as supported by laboratory evidence and in conjunction with neuropsychiatric professionals."[12] Consistent with this stipulation of the appropriateness of IVIG for these disorders, the PANS Research Consortium recommends evaluating children for immunodeficiency because inflammatory and/or autoimmune diseases such as PANDAS and PANS are "more common in patients with immunodeficiency."[6] In other words, children who have immunodeficiency are more at risk for PANDAS and PANS and such testing can confirm an inflammatory or autoimmune process underlying their illness.

The American Society for Apheresis (ASFA) included PANDAS in its guidelines published in the Journal of Clinical Apheresis (JCA) in its last two editions.[13,14] Their 2019 issue provided apheresis indications, including plasmapheresis and IVIG when appropriate, for 84 different diseases based on an extensive review of the literature.[14] When PANDAS was first included in the 2013 issue, the "strong recommendation" for treatment with therapeutic plasma exchange (TPE) by the ASFA set a new precedent given the rigorous, evidence-based methodology of this body.[13] "In severely symptomatic patients with PANDAS or SC, immunomodulatory

therapies, such as IVIG…or TPE, have been shown to be effective in reducing symptom severity or shorten the course." The strong endorsement of immunomodulatory therapies for PANDAS continues in the present edition.

A 2018 review published in the official journal of the European Paediatric Neurology Society evaluated treatment for immune-mediated movement disorders and classified IVIG as a first line therapy in the treatment of PANDAS and anti-NMDA encephalitis.[15.] The authors state that, although the pathophysiological processes differ in these conditions, "there are general themes that broadly apply including: early diagnosis and treatment is better, minimise the severity of disease, escalate treatment if the patient is not responding to initial treatments, and minimise relapse."

Two papers, a treatment study and a literature review were published in quick succession in the Journal of Neurology and Neurosurgery in 2016.[16,17] The treatment study found that up to 84% of pediatric patients exhibited benefit after IVIG and maintained this response even at 12 months.[16] Children with low IgA, IgG, or IgG subclass at baseline were more likely to achieve and maintain 100% improvement at one year. The review expanded on an understanding of inflammatory autoimmune disease: "From immunodeficiency to autoimmunity, the dynamic immunologic basis of PANDAS highlights the broad potential of high-dose IVIG therapy."[17] Their literature search yielded a total of eight studies comprised of 145 children who met PANDAS criteria and received IVIG. On the basis of their systematic analysis, IVIG was deemed to be a "safe and useful adjunctive therapy in the treatment of refractory neuropsychiatric symptoms due to PANDAS and its variants."

Additional recent treatment studies have documented that the response to IVIG is beneficial and appropriate for a subset of children with PANDAS. In an Italian study, 85% of "serious-severe" children with PANDAS showed a reduction or disappearance of the symptomatology following IVIG (1-2 cycles)."[18] For all pediatric participants in a blinded randomized control trial, a 62% mean decrease on the Children's Yale–Brown Obsessive Compulsive Scale (CY-BOCS), maintained at 6 month follow-up, was indicative of improvement.[19]

A 2019 case study published in the British Medical Journal illustrates the profoundly debilitating symptoms of PANDAS in the acute phase and the significant and swift recovery possible when appropriate therapy is administered expeditiously. [20]

> A 6-year-old Indian boy residing in Bahrain was referred to us by his general practitioner (GP) after experiencing 4 days of irritability in the form of increased proneness to anger, which got worse with time, sleep disturbances, severe eating restrictions, parental separation anxiety, emotional lability, personality changes, loss of speech and intermittent eye blinking. The onset of these symptoms was abrupt.…His mother further reported that he refused to eat on the day prior to his admission and was force fed.…Additionally, he injured two of his teeth as a result of his agitated behaviour.[20]

The patient's medical workup revealed an antistreptolysin O (ASO) titer approximately five times above the normal upper limit. Following a diagnosis of PANDAS, the patient received one dose of immunoglobulin (12 hour infusion) and IV ampicillin over the course of his hospital stay. Within 48 hours, all of his symptoms resolved to normal, including behavior, activity level, appetite, and speech. Upon discharge, he was prescribed prophylactic penicillin. The authors concluded, "PANDAS can be rapidly cured with appropriate antibiotics and immunoglobulin administration."[20]

STANDARDS OF MEDICAL PRACTICE AND MEDICAL NECESSITY

Evidenced-based best practices drive the decision-making of physicians as to the efficacy of IVIG to meet the needs of a given patient, and should be the basis of insurers' decision-making when determining authorization. In formulating and adopting medical policies with respect to covered services, it is understood that insurers shall rely on "generally accepted standards of medical practice" or "standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community or otherwise consistent with the standards set forth in policy issues involving clinical judgment."[21,22] This includes the recommendations of physician specialty societies and practicing specialists.

PANDAS Physicians Networks (PPN) in the US and UK represent physician specialty groups for practicing physicians in their respective countries. Their recommendations support a full range of treatment options for children with PANDAS and PANS, including IVIG. In particular, they underscore the favorable risk-benefit ratio for moderately severe to life-threatening cases "because the children's symptoms are causing significant impairment in daily functioning." The guidelines published by the PANS Research Consortium set standards of medical practice to support treating physicians who conclude that IVIG is medically necessary for children who are not responding to other therapies. The findings summarized in this update meet the criteria for medical necessity highlighted in the book, Essential Health Benefits: Balancing Coverage and Cost:[21,22]

> "Medically Necessary" or "Medical Necessity" shall mean health care services that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are: a) in accordance with generally accepted standards of medical practice; b) clinically appropriate, in terms of type, frequency, extent, site and duration, and considered effective for the patient's illness, injury or disease; and c) not primarily for the convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.[21]

PARITY

Although symptoms of these disorders often present as primarily psychiatric, they are a manifestation of a neurological condition. PANDAS and PANS rest at the intersection of mental and physical health, yet these branches of care are not fully aligned and therefore often do not work together in an efficient manner. The stakes are high for children with psychiatric symptoms regardless of their root cause. The cost and the stigma are often crippling for families.

> Children with serious emotional disturbance are among the most fragile members of our society. ... Prompt coordinated services that support a child's continuation in the home can allow even the most disabled child a reasonable chance at a happy, fulfilling life. Without such services, a child may face a stunted existence, eked out in the shadows and devoid of almost everything that gives meaning to life.[23]
>
> U.S. District Court Judge Michael A. Ponsor, Rosie D. v. Romney, January 26, 2006

For families whose children have PANDAS and PANS, the risks are no less significant and the implications of lack of access to adequate treatment are no less serious than in any other mental or physical illness. For children with PANDAS and PANS, parity between mental health coverage and medical health benefits is critical as the most effective intervention is that which not only equates but coordinates behavioral health support with medical evaluation and treatment.

CONCLUSION

The efficacy of immunomodulatory treatment has been rigorously examined since 2015. Recent evidence overwhelmingly supports inclusion of IVIG in the levels of treatment available for children with PANDAS and PANS. Based on extensive systematic reviews from several specialty areas, treatment studies, and the consensus guidelines of the PRC and PPN, IVIG is indicated for the treatment of a small but significant subset of children who meet the criteria.

The current gap in health insurance coverage is causing disruption in physicians' medical practices, as well as an undue financial burden on patients, families, schools, insurers, and communities. When children are significantly impacted or in crisis, medical, mental health, and educational services are required to meet their needs. Parents miss work to care for their children and take them to appointments; insurers pay for ambulance transport, emergency room treatment, and psychiatric hospitalization; and schools place students in special classrooms, provide one-on-one classroom aides, and send tutors to homes when children are unable to attend school. Taking these factors into account, it is not only medically necessary, but cost-effective to provide appropriate treatment to these children without delay. Further, by effectively treating PANDAS, in which psychiatric symptoms stem from an organic illness, physicians can mitigate the lasting impact of infection, inflammation, and/or immune dysfunction on the developing brain, allowing children to recover and regain function in the home, school, and community.

IVIG for the treatment of children with PANDAS and PANS is almost universally denied by commercial Massachusetts insurers. As a result, physicians cannot exercise their best and full clinical judgement in order to provide sufficient care for the most severe patients whose symptoms are extremely impairing and often life-threatening. The appeals process is not structured to include a physician who is an expert in the management of these conditions, and clinicians are frustrated by their inability to objectively discuss IVIG approval with a knowledgeable expert. We ask the insurers' Physicians Advisory Committees and Medical Policy Review Boards to review recent evidence for the efficacy of IVIG in the treatment of PANDAS and PANS, and to support access to a full range of treatment.

Today, severely ill children wait indefinitely for appropriate medical intervention due to the gap in coverage for immune therapy in Massachusetts. Now is the time to change the clinical outcomes for children. Passage of An Act Relative to Insurance Coverage for PANDAS and PANS (H.920/S.613) will ensure that a full range of treatment options is widely available.

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ETHICS CASE

Prescribing "Off-Label": What Should a Physician Disclose?

Commentary by Katrina Furey, MD, and Kirsten Wilkins, MD

Abstract

This case highlights clinical dilemmas faced by physicians when treating patients with conditions for which there are limited or no FDA-approved treatment options. First, it raises questions about when it is appropriate to prescribe medications for "off-label" indications and what might be the ethical and legal implications of doing so. It also prompts us to consider why pharmaceutical companies might or might not pursue FDA approval for new indications when a drug has already been approved for use in another condition. Finally, this case demonstrates the importance of employing shared decision making when discussing complex clinical decisions and how such techniques might have led to different outcomes and better understanding between Dr. Shannin, Maxine, and Heather.

Case

Heather brings her 89-year-old mother, Maxine, to the office of her psychiatrist, Dr. Shannin, for an evaluation. Maxine lives with Heather's family, and though she has been diagnosed with dementia, she still sees Dr. Shannin in his office by herself while Heather waits for her in his office lobby. During her last visit with Dr. Shannin three months ago, Maxine reported that whenever she got confused, she began to think that the people around her were going to harm her. Heather also expressed concerns about Maxine's confusion and paranoia, since Maxine would typically respond to those feelings by acting out as if she were being threatened. Maxine was unable to remember these outbursts, but she did remember feeling agitated and did note that Heather seemed very upset when she felt that way. At that time, Dr. Shannin suggested that Maxine try an atypical antipsychotic, olanzapine, to help control her agitation and paranoia. He explained the risks and benefits in detail and also explained that while he'd had good results with several patients with this medication in the past, managing confusion, agitation, and paranoia was not what this medication is really for. Maxine felt confident that Dr. Shannin had used this medication to manage these symptoms for his other patients, however, and so she agreed to begin taking olanzapine, which has managed her symptoms well for the last three months.

Maxine's dementia has progressed significantly since her last visit with Dr. Shannin, and she is having a particularly bad day today: she doesn't recognize her longtime physician

and is unable to correctly answer questions about being oriented to time and place. It seems that from this point forward, Maxine will no longer be able to participate meaningfully in decisions about her own care, so Heather now takes a more active role in Maxine's care planning and accompanies Maxine during her appointment with Dr. Shannin.

Dr. Shannin asks Heather if she has any questions for him about Maxine. "Yes," she says, "What's olanzapine? I know she's been taking that for a while, but when I looked it up, it seems to be used for treating psychosis. I'm puzzled. My mother's not psychotic." Dr. Shannin explains his rationale. Heather follows his explanation closely and confirms that while Maxine's memory and functioning have declined over the last three months, she appreciates that she has been less confused, agitated, and paranoid. However, Heather worries about her mother continuing to take a drug that's "off-label" and contains a black box warning in the package. "It just doesn't seem safe, particularly since the black box warning notes an increased risk of death," she explains to Dr. Shannin. "I assume you explained the risks to her when she consented to take this medication three months ago. You've taken good care of my mom and I don't doubt your good intentions. But, as a physician, I guess I don't understand how you're really even allowed to prescribe medications in ways that aren't approved by the Food and Drug Administration."

Dr. Shannin wonders how to respond.

Commentary

Approval by the Food and Drug Administration (FDA) implies that available evidence shows that a drug is safe and effective for the specific indication (disease or symptom) for which it was tested [1]. "Off-label" drug use commonly refers to prescribing currently available medication for an indication (disease or symptom) for which it has not received FDA approval [1, 2]. Off-label use also includes prescribing a drug for a different population or age range than that in which it was clinically tested and using a different dosage or dosage form [1, 2]. Contrary to what patients might assume, off-label drug use is not the same as experimental or research use. Once a drug is FDA-approved for a specific indication, legally it can be used for any indication [3, 4]. Off-label prescribing is common; it accounts for 10 to 20 percent of all prescriptions written [5], although the practice is more common in specific patient populations like children and the elderly [1, 2, 5]. Physicians also might be more likely to prescribe off-label medications for patients facing life-threatening or terminal medical conditions for which there are limited or no FDA-approved alternatives [1, 5].

There are several reasons why off-label prescribing is so common. Advances in clinical medical practice often outpace the FDA's ability to approve new drugs or relabel previously approved drugs with new indications [1, 2, 5]. The FDA approves only 40 to 60 percent of all drugs submitted for review, and it can take six to eight years and approximately $1.7 billion to get a new drug approved [4]. Moreover, the revenue

associated with relabeling a drug with additional indications might not offset the expense required to conduct the necessary clinical trials, which discourages most pharmaceutical companies from relabeling drugs once they have already been FDA-approved for one indication [1].

Another reason that off-label prescribing is common is that there is limited evidence of the effectiveness of "on-label" use in certain patient populations frequently excluded from clinical trials, such as children, pregnant women, the elderly, and psychiatric patients [1, 2, 5]. In psychiatric patients, in particular, symptom similarity between disease states might contribute to use of one medication off-label for various conditions [1]. Specifically, off-label use of antidepressants, anticonvulsants, and antipsychotics is high and such use increases in prevalence with patients' advancing age [1, 6]. Elderly patients with dementia, like Maxine, belong to two of the aforementioned groups.

It is important to note that there are no FDA-approved treatment options for dementia-related behavioral disturbances (e.g., psychosis, agitation) [7]. However, randomized controlled trials suggest modest efficacy of atypical antipsychotics in reducing these symptoms [7], and expert consensus and professional guidelines support the use of antipsychotic medications like olanzapine in clinically appropriate circumstances when nonpharmacologic management has failed [8, 9]. In fact, the use of off-label atypical antipsychotics for conditions like dementia has increased in recent years [1]. In Maxine's case, if medications are deemed necessary for behavioral symptom management (i.e., nonpharmacologic management has failed or her symptoms have become significantly distressing or dangerous), it is reasonable from clinical and ethical standpoints for Dr. Shannin to prescribe olanzapine off-label for her.

Legalities of Off-Label Prescription Drug Marketing and Use

Physicians like Dr. Shannin might worry about legal implications of prescribing off-label. It is important to remember that though FDA approval is based on available evidence of the effectiveness and safety of a drug for the specific indication for which it was tested, it does not guarantee either, even for on-label uses [4]. For example, the FDA has approved drugs, like Vioxx, that were actually unsafe for on-label uses [3]. Because of the associated risks, the FDA has limited manufacturer marketing of off-label uses of FDA-approved drugs [1, 4]. The FDA Modernization Act of 1997 [10] ruled that manufacturers are allowed to distribute peer-reviewed journal articles about off-label uses of medications to health care professionals upon request [1]. Such off-label drug use publications must be accurate and unedited, and the relationship between information distribution and the sponsoring pharmaceutical company must be clearly disclosed in the marketing materials [1]. The FDA has continued to ban direct-to-consumer marketing of off-label uses by preventing such indications from being advertised in package inserts, TV advertisements, or patient education materials [1]. Nevertheless, off-label marketing by pharmaceutical companies has been one of the most common causes of Medicaid fraudulent claim investigations [11].

The FDA does not prohibit physicians from prescribing drugs off-label [4], and Congress has repeatedly taken legal steps to prevent the FDA from interfering with the practice of medicine [4]. Although many malpractice lawsuits have been filed on behalf of patients arguing that they did not give informed consent to take a drug because they were not informed that use for their particular condition was actually off-label, the law has generally sided with physicians in finding that they have no legal duty to inform patients of a drug's regulatory status [3, 4]. Such rulings enforce that off-label is an FDA regulatory term that denotes nothing about clinical risks or benefits [4]. The physician's duty is to provide *clinical* information and some have argued that taking the time to explain the legal complexities of FDA approval versus off-label drug use could distract from shared clinical decision making [3, 4].

Weighing the Evidence

Because physicians often treat clinically complex patients, they must balance a patient's needs and individual characteristics with available scientific evidence when deciding whether to prescribe medications off-label [5]. Off-label use is appropriate when it is in the best interest of the patient on the basis of credible, published scientific data supporting the use of the drug in that manner [1, 5]. Furthermore, the risks of using a medication off-label should not outweigh the benefits, although this distinction might be less clear in complicated situations or for patients with many comorbidities [5].

Atypical antipsychotics used off-label to treat dementia-related behavioral disturbances carry significant risks, which, some have argued, outweigh their benefits [12]. The risks posed to Maxine by using olanzapine include general risks to all patients taking antipsychotics (e.g., parkinsonism, akathisia, tardive dyskinesia, metabolic syndrome) as well as risks specific to patients with dementia (e.g., stroke) [13]. In addition, all antipsychotic medications carry a black-box warning of increased risk of death compared to placebo in patients with dementia [13]. In this case, the risks of using olanzapine off-label must be weighed against the risks of not treating Maxine's escalating paranoia and agitation. Untreated behavioral symptoms of dementia have been associated with an increased risk of nursing home placement and higher rates of caregiver burden, which could lead to decreased quality of life for Maxine and her daughter [7]. Some studies have also shown that dementia-related psychosis and agitation have been associated with more rapid cognitive decline and an increased mortality risk [7].

Shared Decision Making

A key question in this case is whether Maxine had decisional capacity to consent to the initial prescription of olanzapine. She accepted the medication after a discussion of risks and benefits, likely because of her trust in Dr. Shannin. The power dynamic in physician-patient relationships can be such that patients and families trust their physician implicitly; this has its merits and drawbacks, from clinical and ethical standpoints. Although Dr. Shannin indicated to Maxine that he was using olanzapine to treat a

condition for which it was not originally intended, he did not specifically disclose to Maxine its lack of FDA approval to be used to treat her specific symptoms. As discussed above, he is not legally required to do so, but, from an ethics point of view, we might still wonder how his nondisclosure might have affected his alliance with Maxine and Heather. For example, Heather was surprised to learn that her mother had been prescribed a medication typically used in patients with psychotic disorders. Given Maxine's cognitive decline, Heather will likely be assuming a much greater role in medical decision making. Will she trust Dr. Shannin to fully disclose treatment risks in the future? A potential worry is that if nondisclosure undermines Heather's trust in Dr. Shannin, she might not feel comfortable reaching out to him in a crisis or when her mother's treatment needs escalate.

The practice of patient-centered medicine requires that patients and families experience medical treatment decisions as a collaborative and shared process. In his initial discussion with Maxine about olanzapine, Dr. Shannin could have employed additional communication strategies that are key to shared decision making. Whether or not a patient with dementia has decision-making capacity, it is reasonable to ask the patient's permission to include a trusted family member in discussion of treatment options. Maxine might not later recall specific details of the conversation, and, given the typical progressive decline of patients with dementia, she will likely need increasing family involvement in the future. Bringing a family member into the discussion allows a physician to inquire about the effects of the symptoms on the patient's and family's quality of life and to ascertain specific treatment goals of a patient and her family, which might not always be congruent with those of the physician. In this case, Dr. Shannin's goal could be to ensure Maxine's safety and to reduce caregiving burden on Heather. However, Maxine might want a medication to calm her nerves or help her sleep, and Heather might want to reduce familial stress or delay Maxine's placement in a nursing home.

How can shared decision making be implemented? Elwyn et al [14] propose a practical three-step communication model for shared decision making: (1) "choice talk," the step at which patients are made aware that reasonable options exist; (2) "option talk," the step at which patients are provided information about the options; and (3) "decision talk," the step at which patients are supported in considering preferences and making a decision. In this case, if Maxine had not yet been treated for her symptoms, choice talk might include making Maxine and Heather aware that both nonpharmacologic and pharmacologic treatment options exist for agitation and paranoia in dementia. Option talk could include Dr. Shannin's noting that pharmacologic options are limited and that no medications are FDA-approved for this indication. He could then discuss the risks, benefits, and off-label use of olanzapine, and provide a lay summary of the scientific evidence and practice standards that guide use of this medication despite its lack of FDA approval in dementia. Dr. Shannin could also explain nonpharmacologic alternatives (e.g.,

patient reassurance and redirection) and pharmacologic alternatives (e.g., antidepressants) to olanzapine. Option talk might also make use of decision support aids such as pamphlets, videos, or reputable websites, which have been shown to lead to improved patient knowledge, more accurate perception of risks and benefits, and greater participation in decision making [15]. The idea is that patients are supported in the deliberation process throughout and given ample time to make a final decision, which can take more than one encounter [14].

Conclusion

Off-label prescribing is a common and legal practice in medicine. This practice is justified when scientific evidence suggests the efficacy and safety of a medication for an indication for which it does not have FDA approval and when the practice is supported by expert consensus or practice guidelines. Through shared decision making, patients and families are equal partners in clinical decision-making processes, which can help a physician carefully weigh risks and benefits of a given treatment according to the patient's unique circumstances.

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