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Another Arrow in our Quiver: a Role for Anti-Inflammatory Therapies in Mental Health Treatment for Pediatric Patients

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ABSTRACT

The prevalence of pediatric depression and anxiety has surged dramatically, particularly in the wake of the COVID-19 pandemic, exposing limitations in existing mental health treatments. Traditional therapies of psychotropics and psychotherapies often yield suboptimal results due to limited efficacy, tolerability concerns, poor adherence, and treatment resistance. Emerging evidence suggests neuroinflammation may drive treatment-resistant psychiatric symptoms in youth, particularly in cases of sudden-onset symptoms and post-infectious presentations. In this select group of patients, anti-inflammatory therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs), antihistamines, corticosteroids, and intravenous immunoglobulin (IVIG), show promise as adjunctive and/or alternative interventions, potentially providing symptom relief and improved tolerability compared with psychotropics. Though behavioral therapy and psychotropics like selective serotonin reuptake inhibitors (SSRIs) remain a mainstay of treatment, anti-inflammatory therapies represent a promising "arrow in the quiver," especially in cases where antidepressants are insufficient or contraindicated; NSAIDs in particular may provide safe and rapid symptom relief. Further research is needed to establish treatment protocols and guide clinicians in providing personalized care for neuroimmune-linked psychiatric disorders in youth; however, we aim to help fuel this important conversation and encourage clinicians to begin considering anti-inflammatory therapies as part of their clinical toolkit.

I. Introduction

The prevalence of depression and anxiety among children and adolescents has risen over the last few decades, and nearly doubled since the beginning of the COVID-19 pandemic. Pooled estimates indicate that 25.2% of youth globally now experience clinically significant depression symptoms and 20.5% experience anxiety, compared to 11.6% and 12.9% respectively before the pandemic.[1] Current treatment modalities for managing psychiatric symptoms in pediatric patients include psychotherapies, psychotropic medications, and lifestyle modifications; however for a variety of reasons, including high rates of inadequate treatment response, insufficient access to specialists, parental reluctance to accept psychotropic treatments, poor compliance, and concerns regarding tolerability and abuse potential, these treatments are not sufficiently addressing patient needs. Further, long-term administration of psychotropic treatment in children poses special considerations for this vulnerable population.[2, 3]

Here we discuss the rationale for including anti-inflammatory treatments as additional "arrows in our quiver" in addressing these challenges, particularly, but not exclusively, for patients whose symptoms appear in the context of known or likely immune dysfunction, for those with sudden-onset symptoms without a known psychological trigger, and/or for those who are resistant to conventional treatments. These therapies could serve as alternatives or adjuncts to traditional psychiatric treatments. This discussion is timely given that increasing evidence suggests that post-infectious inflammation plays a significant and underappreciated role in the dramatic increase in psychiatric symptoms in youth post-COVID: psychosocial stressors such as social isolation, academic disruption, and family financial instability are likely not the sole drivers of this trend.[1, 4]

II. The Relationship between Inflammation & Psychiatric Symptoms

Although associations between inflammation (including infection-related) and psychiatric symptomatology have been recognized for centuries, increasing direct evidence has shed light on the nature of this relationship. It is fairly well-established that infectious diseases and inflammation may trigger the onset of psychiatric symptoms in specific subsets of child and adult patients, including individuals with elevated immune mediators (e.g. increased levels of proinflammatory cytokines like IL-6, TNF-α, IL-1β), persistent immunological impairment, treatment-resistant psychiatric diseases, autoimmune or neuroinflammatory processes, or post-infectious syndromes like Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Long COVID.[5-8]

In addition, multiple lines of evidence—including physiological studies of broad populations of psychiatric patients and high rates of comorbidity between psychiatric and immunologic disorders[9,10,11]—suggest that immunological contributions to psychiatric morbidity may be much greater than is currently recognized. For example, pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α are often elevated in Major Depressive Disorder (MDD) and other psychiatric disorders in adults,[5] and elevated levels have also been reported in children and adolescents with psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD).[6] Early-life immune dysregulation may also play a role; prenatal exposures to maternal autoimmune diseases and common infections are associated with increased risk of OCD, schizophrenia, mood disorders, and neurodevelopmental disorders in offspring.[22, 23] Inflammation can contribute to psychiatric symptoms through pathways such as blood-brain barrier disruption, allowing peripheral cytokines to access the central nervous system and alter neurocircuitry involved in mood and cognition.[5]

Importantly, individual differences in baseline cytokine levels have been shown to predict treatment response. In one study of 24 MDD patients and 15 controls, all patients had elevated TNF-α levels at baseline. However, those with lower IL-6 levels at baseline were more likely to respond to SSRI treatment—showing significant improvement in

depressive symptoms, as measured by the Hamilton and Montgomery-Asberg Depression Rating Scales (HAM-D). Among responders, TNF-α levels significantly decreased during treatment, whereas non-responders did not show such change.[5] These findings align with broader evidence that some psychiatric medications—including antidepressants, antipsychotics, and mood stabilizers—have anti-inflammatory properties, reducing pro-inflammatory cytokines such as IL-6 and TNF- α, which may contribute to their therapeutic benefits.[12]

Anti-inflammatory treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), intravenous immunoglobulin (IVIG), steroids, and antihistamines appear to be effective in managing neuropsychiatric conditions with a presumed neuroimmune basis and, to some extent, neuropsychiatric conditions more broadly.[13,14] These therapies act through various mechanisms to reduce inflammation: NSAIDs inhibit cyclooxygenase (COX) enzymes and reduce pro-inflammatory prostaglandins; IVIG modulates immune signaling and suppresses autoantibody activity; corticosteroids suppress widespread immune responses by downregulating cytokine production; and antihistamines block histamine receptors involved in inflammatory signaling. Not surprisingly, NSAIDs significantly reduce psychiatric symptoms and shorten the duration of flare-ups in patients with PANS,[7] and for patients with Long-COVID, antihistamines have shown promise in alleviating cognitive symptoms.[8] However, anti-inflammatory treatments have also been shown to effectively manage psychiatric symptoms in a range of other conditions, beyond infection-associated chronic conditions (IACCs), like schizophrenia, bipolar disorder, depression, and OCD.[5,7,14]

In multiple randomized controlled trials, cytokine inhibitors and nonsteroidal anti-inflammatory medications (NSAIDs) have each demonstrated antidepressant therapeutic effects as monotherapies or in combination with other treatments.[5,13,15] For example, several double-blind, placebo-controlled trials with moderate sample sizes (approximately 40 participants per group) have shown that celecoxib, a COX-2 inhibitor and NSAID, significantly enhances treatment response when combined with antidepressants such as reboxetine, sertraline, or fluoxetine in patients with MDD. These studies reported no significant adverse effects, although this may be due to the relatively short treatment durations, which ranged from 6-8 weeks.[5]

III. Benefits, Risks, and Limitations of Psychotropic Medications

Despite sizable research investment, response rates for established psychotherapies and psychotropic pharmacotherapies remain stubbornly below 50%–70% in adults and effect sizes are often limited.[16,5,18] Although research involving children is more limited and often contradictory, meta-analyses suggest that for most antidepressants, effect sizes may be even smaller in pediatric populations than in adults.[17,18]

Medications such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with various adverse effects, including short term effects such as gastrointestinal symptoms (e.g., nausea, abdominal pain), sleep-related symptoms (e.g., insomnia, fatigue, tiredness, vivid dreaming), activation (e.g., hyperactivity, irritability, anxiety), and other symptoms (e.g., headaches, hyperhidrosis, dry mouth, weight gain) and long-term effects like weight gain and disordered sleep.[2] Risk of an increase in suicidal ideation or attempts in youth is also of notable concern and has increased caution in providers in the decision to prescribe such medications to adolescents.[2,3]

Pediatric patients also are more vulnerable to Antidepressant Withdrawal Syndrome (AWD) than adults. AWD, also known as antidepressant discontinuation syndrome (ADS), refers to a group of symptoms that typically occur following the discontinuation, interruption, or significant reduction of an antidepressant medication.[2] These withdrawal symptoms, including irritability and mood swings, tend to be more severe in children and adolescents.

Missing a single dose of longer half-life antidepressant medications like sertraline or escitalopram can cause significant decreases in serum levels. These risks are all the more concerning given the limited research that has been applied to this area. While some randomized controlled trials in pediatric populations have examined antidepressant discontinuation, evidence remains insufficient to establish standardized, evidence-based withdrawal strategies that adequately account for the course of relapse, withdrawal symptoms, and the pharmacokinetic and pharmacodynamic properties of antidepressants.[2, 21]

It is undeniable that medications such as SSRIs and SNRIs play a critical role in the treatment of psychiatric conditions in adolescents. However, there are notable concerns about safety and tolerability and lack of effectiveness for subsets of the clinical population. Antidepressant medications may take four to eight weeks to show effectiveness. For many children a different route of treatment may be indicated in order to prevent side effects and/or discontinuation effects. As Leichsenring et al note, a paradigm shift seems necessary to improve utilization of psychotropic medications, particularly in children who present with sudden-onset symptomatology where an immunological trigger seems likely.[16]

IV. Integrating Anti-inflammatory Therapies into Treatment Protocols

We suggest that clinicians consider trials of anti-inflammatory therapies for patients with inflammatory diagnoses or labs and/or significant family histories, for whom the onset of symptoms was coincident with a known or suspected infection, for whom parents are unwilling to consider psychotropic medications but willing to consider NSAIDS and/or antihistamines, and those who are refractory. At the very least, clinicians should consider more aggressive evaluation and treatment of inflammatory conditions and recurrent or chronic infections when psychiatric symptoms are also present.

Integrating anti-inflammatory therapies into pediatric psychiatric care protocols may offer several benefits. NSAIDs such as ibuprofen and naproxen have well-established safety profiles when properly dosed and monitored[19], and can provide rapid symptom relief—sometimes within hours or days. While side effects such as renal toxicity and gastrointestinal issues can occur, they are generally manageable and the risk of severe adverse effects is low.[5,7] Given their favorable safety profiles, NSAIDs may be better-tolerated than psychotropic medications for select patients, and may represent a treatment approach that these patients and their caregivers may be more willing to consider.[20,14] Additionally, NSAIDs and/or antihistamines can be considered as adjunct therapies to psychotropic medications for patients with inflammatory profiles.[13]

In more severe or treatment-refractory cases, particularly those in conditions such as PANS and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), immunomodulatory treatments (e.g. IVIG, corticosteroids, and plasmapheresis) may be appropriate. Although these treatments can be more invasive or costly than NSAIDs, they can be effective in select cases, especially when individually tailored to patients' symptom severity and clinical course. Before initiating such therapies, a comprehensive evaluation for inflammatory, infectious, and metabolic contributors is recommended.[7]

The early use of anti-inflammatory therapies also holds promise in improving long-term outcomes, especially for pediatric patients with suspected neuroimmune-related psychiatric symptoms who fail to respond to first-line treatments.[7] Emerging evidence suggests that inflammation may precede the full diagnostic criteria for psychiatric disorders, making early intervention a potential strategy to prevent the onset of psychiatric conditions later in life.[6] By addressing inflammation early, clinicians may prevent further central nervous system (CNS) damage, as chronic inflammation can lead to neurotransmitter imbalances and neurodegeneration.[5]

It is important to emphasize that we are not suggesting that anti-inflammatory therapies replace

conventional psychiatric treatments. Even for IACCs with known response to anti-inflammatory treatments, conventional psychiatric and behavioral therapies remain essential treatment components for many patients.[7] Often a combination of antidepressants and NSAIDs produces the best results when initial antidepressant therapy fails, although NSAIDs alone may also demonstrate antidepressant effects in patients with inflammatory comorbidities.[5,15]

V. Conclusion

The growing body of evidence linking inflammation to psychiatric symptoms highlights the potential value of integrating anti-inflammatory therapies into psychiatric care. Anti-inflammatory treatments may provide a viable adjunct and/or alternative to conventional interventions, reduce treatment delays, and improve patient outcomes. However, further research is necessary to establish clear guidelines for their use in pediatric populations. A better definition of non-responders to conventional psychotherapeutics could elucidate a population with neuropsychiatric symptoms driven by inflammatory causes who may benefit from anti-inflammatory approaches. Clinical trials focused on NSAIDs, COX-2 inhibitors, and other anti-inflammatory and immunomodulatory agents, either as adjunctive care or second-line treatment modalities, are essential for developing personalized, affordable, and safe treatment strategies for pediatric populations.

Conflicts of Interest Statement:

The authors have no conflicts of interest to declare.

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References:

1. Racine N, McArthur BA, Cooke J, et al. Global prevalence of depressive and anxiety symptoms in children and adolescents during COVID-19. JAMA Pediatr. 2021;175(11):1–10. doi:10.1001/jamapediatrics.2021.2482

2. Strawn M, Mills A, Poweleit E, et al. Adverse effects of antidepressant medications and their management in children and adolescents. Pharmacotherapy, 2023;43(7):675-690. doi:10.1002/phar.2767

3. Goodman WK, Murphy TK, Storch EA. Risk of adverse behavioral effects with pediatric use of antidepressants. Psychopharmacology (Berl). 2007;191(1):87-96. doi:10.1007/s00213-006-0642-6

4. Wang S, Chen L, Ran H, et al. Depression and anxiety among children and adolescents pre and post COVID-19: A comparative meta-analysis. Front Psychiatry. 2022;13:917552. doi:10.3389/fpsyt.2022.917552

5. Feltes P, Doorduin J, Klein H, et al. Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. Psychopharmacol, 2017; 31(9):1149-1165. doi:10.1177/0269881117711708

6. Malys MZ and Mondelli V. Could anti-inflammatory interventions earlier in development confer primary prevention of psychiatric disorders? Harvard Rev Psychiatry, 2022;30(1):4-7. doi:10.1097/HRP.0000000000000318

7. Frankovich J, Swedo S, Tanya M, et al. Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies. J Child Adolesc Psychopharmacol, 2017;27(7):574–593. doi:10.1089/cap.2016.0148

8. Kazama, I. Brain Leukocytes as the Potential Therapeutic Target for Post-COVID-19 Brain Fog. Neurochemical Research, 2023; 48(8): 2345–2349. doi:10.1007/s11064-023-03912-0

9. Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. J Psychosom Res. 2002;53(4):873-876. doi:10.1016/s0022-3999(02)00309-4

10. Mataix-Cols D, Frans E, Pérez-Vigil A, et al. A total-population multigenerational family clustering study of autoimmune diseases in obsessive-compulsive disorder and Tourette's/chronic tic disorders. Mol Psychiatry. 2018;23(7):1652-1658. doi:10.1038/mp.2017.215

11. Endres D, Pollak TA, Bechter K, et al. Immunological causes of obsessive-compulsive disorder: is it time for the concept of an "autoimmune OCD" subtype?. Transl Psychiatry. 2022;12(1):5. Published 2022 Jan 10. doi:10.1038/s41398-021-01700-4

12. Patel S, Keating BA, Dale RC. Anti-inflammatory properties of commonly used psychiatric drugs. Front Neurosci. 2023;16:1039379. doi:10.3389/fnins.2022.1039379

13. Kohler O, Krogh J, Mors O, Benros ME. Inflammation in Depression and the Potential for Anti-Inflammatory Treatment. Curr Neuropharmacol. 2016;14(7):732-742. doi:10.2174/1570159x14666151208113700

14. Fitton R, Sweetman J, Heseltine-Carp W, van der Feltz-Cornelis C. Anti-inflammatory medications for the treatment of mental disorders: A scoping review. Brain Behav Immun Health. 2022;26:100518. doi:10.1016/j.bbih.2022.100518

15. Fond G, Hamdani N, Kapczinski F, et al. Effectiveness and tolerance of anti-inflammatory drugs' add-on therapy in major mental disorders: a systematic qualitative review. Acta Psychiatr Scand. 2014;129(3):163-179. doi:10.1111/acps.12211

16. Leichsenring F, Steinert C, Rabung S, and Ioannidis JP. The efficacy of psychotherapies and pharmacotherapies for mental disorders in adults: an umbrella review and meta-analytic evaluation of recent meta-analyses. World Psychiatry, 2022;21(1):133-145. doi:10.1002/wps.20941

17. Feeney A, Hock R, Fava M, Hernandez Ortiz JM, et al. Antidepressants in children and adolescents with major depressive disorder and the influence of placebo response: A meta-analysis. J Affective

Disorders. 2022;305:55-64. doi:10.1016/j.jad.2022.02.074.

18. Cuijpers P, Karyotaki E, Ciharova M, et al. The effects of psychological treatments of depression in children and adolescents on response, reliable change, and deterioration: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry. 2023; 32:117-192. doi:10.1007/s00787-021-01884-6

19. Litalien C, Jacqz-Aigrain E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. Paediatr Drugs. 2001; 3(11):817-858. doi:10.2165/00128072-200103110-00004

20. Al-Haidar FA. Parental attitudes toward the prescription of psychotropic medications for their children. J Family Community Med. 2008;15(1):35-42.

21. Stimpfl JN, Walkup JT, Robb AS, et al. Deprescribing Antidepressants in Children and Adolescents: A Systematic Review of Discontinuation Approaches, Cross-Titration, and Withdrawal Symptoms. J Child Adolesc Psychopharmacol. 2025;35(1). doi:10.1089/cap.2024.0099

22. He H, Yu Y, Liew Z, et al. Association of Maternal Autoimmune Diseases With Risk of Mental Disorders in Offspring in Denmark. JAMA Netw Open. 2022; 5(4):e227503. doi:10.1001/jamanetworkopen.2022.7503

23. Suleri A, Rommel AS, Neumann A, et al. Exposure to prenatal infection and the development of internalizing and externalizing problems in children: a longitudinal population-based study. J Child Psychol Psychiatry. 2024;65(7):874-886. doi: 10.1111/jcpp.13923

