Article

Treating ADHD and Comorbid Anxiety in Children: A Guide for Clinical Practice

Clinical Pediatrics
2023, Vol. 62(1) 39–46

DOI: 10.1177/00099228221111246
journals.sagepub.com/home/cpj
SAGE

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is frequently comorbid with anxiety disorders with rates as high as 25% to 50% in children and adolescents. Despite various treatment options for ADHD symptoms, limited research addresses treatment in the context of comorbidity. This article seeks to provide a review of the evidence regarding treatment of this comorbid population. Distinct emotional, cognitive, and behavioral symptoms have been observed in this population, suggesting a need for tailored treatment. Despite common concerns about anxiety exacerbation, stimulant medications demonstrate good tolerability and good response in addressing symptoms. Atomoxetine has also demonstrated some benefit and good tolerability for treating this comorbid population. Selective serotonin reuptake inhibitors can be used as adjunctive treatment for anxiety but require careful monitoring of side effects. Cognitive behavioral therapy (CBT) is an important treatment to improve anxiety symptoms in the absence of significant ADHD symptoms. Psychosocial interventions are also essential to improve outcomes.

Keywords

ADHD, anxiety, comorbidity, treatment, pharmacology, psychosocial interventions

Introduction

Attention-deficit hyperactivity disorder (ADHD) is characterized by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM*-5) as inappropriate levels of inattention, impulsivity, and hyperactivity that surface in childhood resulting in multiple impairments.[1] Anxiety disorders are characterized by a fear which is out of proportion to a situation and that affects normal functioning.[1] These 2 disorders common to the pediatric population are frequently comorbid in rates from 25% to 50%.[2-4] In an Australian sample of 389 participants, 64% of children with ADHD had at least one anxiety disorder, including social (48%), generalized (34%), and separation (32%) anxiety disorders.[4] In addition to the epidemiological significance, some data attest to the substantial clinical burden posed by this comorbidity.[4] Children with ADHD often have difficulty with concentration, executive function, and organization.[4] Although the comorbid population demonstrates decreased hyperactivity and impulsivity compared to ADHD-only, children with both ADHD and anxiety may experience greater mood and executive dysfunction.[4] Given the clinical relevance of this relationship, early recognition and treatment are important.[5,6] A recent revision of the American Academy of Pediatrics guidelines underscores the importance of routine assessment of comorbid disorders.[7] Controversy has persisted however, regarding the proper treatment of this population due to potential anxiogenic effects of stimulants in children with anxiety disorders. In addition, selective serotonin reuptake inhibitors (SSRIs), which are the first-line pharmacological treatment for anxiety disorders, may cause activation and suicidal ideation in the pediatric population.[8] Furthermore, even when pharmacotherapy does lead to symptom improvement, there may not be a corresponding improvement in function at home or at school. For all these reasons, it is important to look at the use of psychosocial and therapeutic interventions to enhance the effective treatment of these children.[4]

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Methods

An independent search of *PubMed* databases was carried out. Keywords included: ADHD, anxiety, comorbidity, treatment, psychopharmacology, children, adolescents, and cognitive behavioral therapy (CBT). Date rage included in search was from inception through June 2020. Filters for reviews, systematic reviews, clinical trials, and randomized clinical trials were applied prior to screening. These 1458 articles were screened manually by their title for appropriateness. Three of the authors screened these records manually. Initially, articles were reviewed independently and subsequently as a team. Articles needed to focus specifically on comorbid ADHD and anxiety in the pediatric population. Articles were reviewed and included/excluded as outlined in Figure 1. We would like to highlight that we did not include an article that focused on desipramine, as it is rarely used in clinical practice due to reports of sudden death in children.[10] A limitation of our review is that only articles that were available in *PubMed* were included. It is possible there are additional articles that discuss this comorbidity that do not appear on a *PubMed* search.

Effect of Anxiety on Clinical Presentation of ADHD

Studies have generally shown that elevated levels of anxiety may exacerbate cognitive and emotional dysfunction.[11] The presence of anxiety may make children with ADHD present as more inattentive and less impulsive.[12,13] In addition, children with this comorbidity exhibit fewer conduct and aggressive symptoms.[14,15] Such children displayed lower activity in the cerebellum, striatum, and thalamus during working memory tasks relative to ADHD alone.[16] This suggests a different subtype of ADHD with distinct pathogenesis.[14,15,17,18] Conversely, some argue that anxiety is only a consequence of ADHD-based impairments. Anxiety in children with ADHD may be related to their inability to function in other aspects of their daily life due to ADHD symptoms.[19] It is possible that this anxiety worsens cognitive performance, but this is not entirely clear.[13,15] Supporters of this theory suggest the anxiety in ADHD patients originates from worrying about academic tasks.[19] In either case, heightened executive dysfunction and inattention likely explain the impairments seen in these patients.

Neuropsychological functioning is also altered in this population.[20] Response inhibition allows a person to engage in adaptive behaviors rather than act impulsively.[21] Deficits in response inhibition are often seen in ADHD. Stop signal tests are the classic measurement of response inhibition.[3,18,19,22] These tests typically consist of concomitant tasks in which the person receives a signal to stop or to proceed with a specific task. Children with ADHD and anxiety demonstrate improved performance on stop signal tests when compared to those in other ADHD subgroups.[23,24] Studies have demonstrated less impulsivity in these comorbid patients compared to other ADHD subgroups.[22] Children with ADHD and comorbid oppositional defiant or conduct disorder were more impulsive when compared to comorbid anxiety patients, suggesting that anxiety decreases impulsivity in ADHD patients.[23]

Studies have further attempted to quantify level of impairment in this population. A 2014 study examined the impact on quality of life and function in comorbid ADHD/anxiety.[4] Results indicated decreased academic functioning in children with ADHD and 2 or more anxiety disorders.[4] These findings imply that magnification of functioning difficulties may be present only in those with severe anxiety. Regardless, treatment of this comorbidity has the potential to improve outcomes.

Pharmacological Treatment

Medications frequently used for ADHD fall into 2 categories: stimulants (e.g., methylphenidate [MPH]) and nonstimulants (e.g., atomoxetine [ATX]). The first-line pharmacotherapy for childhood anxiety is SSRIs.[25] Most studies on the pharmacological treatment of ADHD and anxiety in the pediatric population focus on these agents. A summary of treatment recommendations for this population is presented in Table 1.

Stimulant Medications

Stimulant medications are a first-line treatment for ADHD.[26] While response rates can vary, concomitant intensive psychosocial intervention can improve outcomes, especially in children with comorbid anxiety.[27] Still, controversy remains with using stimulants in this population. Package labels indicate anxiety as a relative contraindication to this treatment, raising concerns about exacerbation of symptoms. Physician concerns may also arise from a lack of familiarity on safe implementation of treatment.[28] Moreover, parents may resist medications, citing the potential for addiction or adverse effects. Despite this, stimulants are a cornerstone in adequate management and other treatments, such as psychosocial interventions, may not be effective prior to medication management.

Methylphenidate is the gold-standard treatment in ADHD, with extensive research supporting its efficacy in children and adolescents. However, efficacy in treating

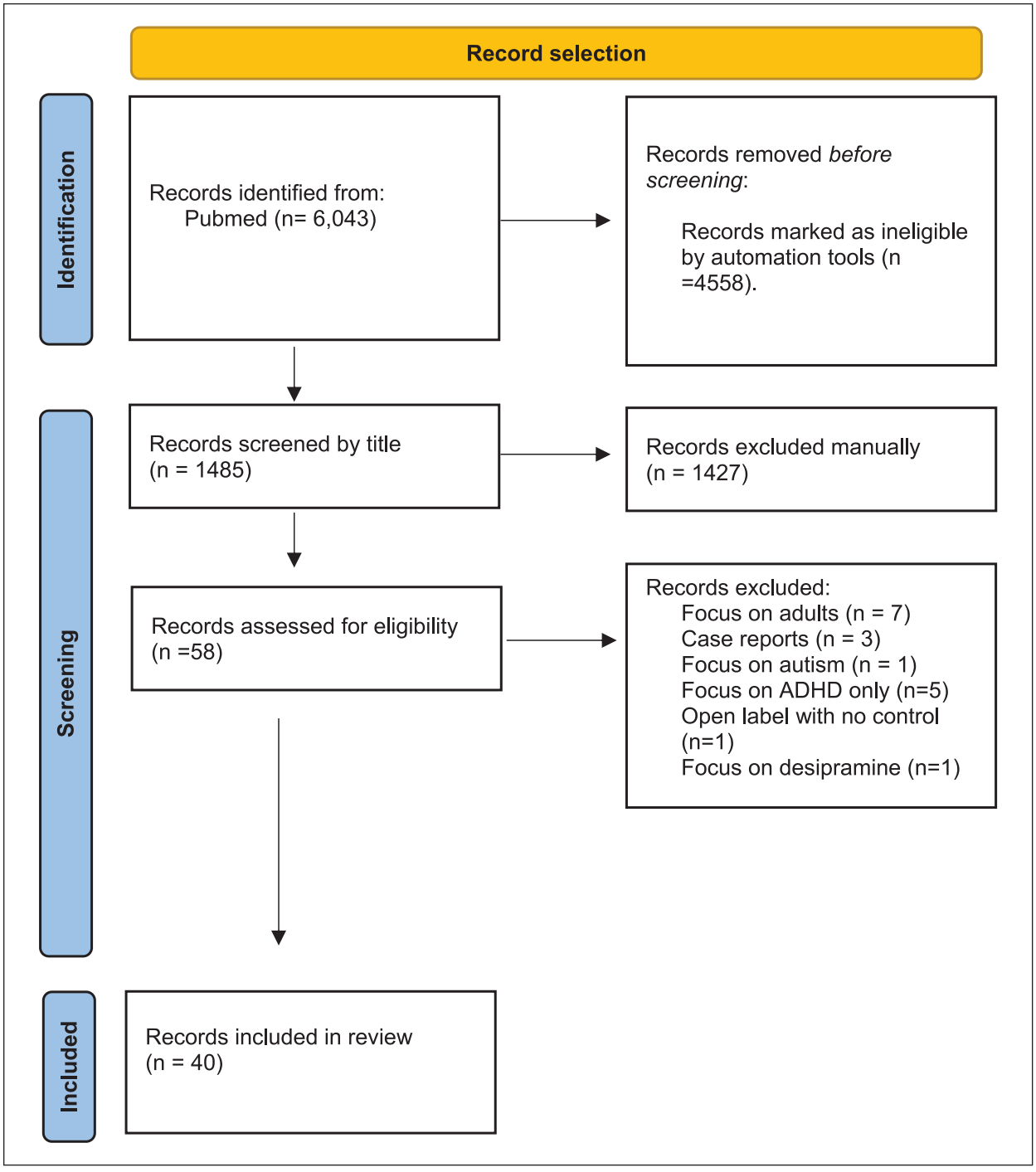

Figure 1. Study selection.
Source: Page et al.[9]
Abbreviation: ADHD, attention-deficit hyperactivity disorder.

comorbid anxiety has remained in question. Early studies indicated a correlation between the presence of anxiety in ADHD and a decreased response to MPH. In a double-blind trial of MPH (N = 43), children with comorbid anxiety had a significantly reduced response compared to nonanxious controls.[29] Another double-blind, placebo-controlled, crossover study evaluated the effects of MPH on working memory and activity level in anxious versus

Table 1. Summary of Treatment Recommendations for Pediatric ADHD and Anxiety.

Population	Medication	Comments
ADHD > Anxiety	MPH	CBT helpful for residual anxiety
ADHD < or = Anxiety	Atomoxetine	CBT, ±BPT
ADHD + severe and/or treatment resistant anxiety	Atomoxetine OR MPH + fluoxetine	CBT may be of greater benefit than fluoxetine though head-to-head studies are lacking.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; MPH, methylphenidate; CBT, cognitive behavioral therapy; BPT, behavioral parent/teacher training.

nonanxious ADHD children.[17] Forty ADHD children (22 nonanxious, 18 anxious) received 3 doses (0.3, 0.6, and 0.9 mg/kg) of MPH.[17] Measures included a serial addition task to assess working memory and behavioral observations to assess activity level.[17] Results suggested MPH reduced hyperactivity equally in both groups, but a differential response was found for working memory.[17] Working memory improved to a larger degree in ADHD-only controls compared to the comorbid group.[17] This is consistent with high levels of working memory impairments seen in this population.[16] Similarly, other researchers examined variables predicting response to MPH in ADHD children and found low levels of anxiety to be a robust predictor of positive response to MPH. However, the finding that highly anxious children are less responsive to MPH was not replicated in subsequent studies.[30]

A 1999 study evaluated whether anxiety altered MPH efficacy for pediatric ADHD.[31] Ninety-one children with ADHD were stratified by having ADHD versus ADHD/anxiety.[31] Thirty-eight out of 91 children met criteria for comorbid anxiety disorders.[31] Participants were treated with MPH immediate release (IR) over a 4-month period on a titration schedule to a standard dosage of 0.7 mg/kg.[31] Parental and teaching rating scales were used to measure changes in the children's aggression, hyperactivity, and inattention at baseline, after titration, and at 4-month follow-up.[31] This study showed no difference in response to MPH between these groups initially and at 4 months in any of the measures.[31] Moreover, a 2015 trial showed a decrease in anxiety symptoms with MPH.[32] Of note, the sample only included children with subdiagnostic anxiety and may not be generalizable to children with severe anxiety.[32]

An open-label Israeli study evaluated the response of subsyndromal separation anxiety to MPH in children with ADHD (N = 42) over 12 weeks.[33] Methylphenidate was associated with a decrease in separation anxiety, as well as improvement in ADHD symptoms.[33] The investigators also evaluated the effects of MPH on social phobia symptoms and ADHD.[34] Twenty-one children with ADHD and social phobia received MPH for 12 weeks, resulting in substantial improvements in ADHD and social phobia symptoms at its conclusion.[34] Nearly all participants responded regardless of severity of social phobia.[34] However, controlled studies are needed to replicate these findings. Tolerability of MPH in this population has also received attention. One initial study suggested that comorbid ADHD/anxiety may make children more susceptible to side effects of MPH treatment.[17] In this study, a greater heart rate increase with low dose (0.3 mg/kg) MPH was seen after 1 hour of administration.[17] However, fixed doses of MPH were used without a titration schedule, which is not reflective of clinical practice. Other studies using titration schedules did not show increased side effects.[31,35,36] Available evidence suggests that MPH has some efficacy and good tolerability for treatment of this comorbid population.[31,35,36] Pediatricians are advised to use their clinical judgment in making the decision whether to start MPH. It is reasonable to start MPH in children with a careful titration schedule and monitoring for worsening of anxiety and other side effects.[10] In addition, the principle of "start low and go slow" may be useful to assess the effects of MPH on anxiety symptoms. Methylphenidate appears to be a good first choice particularly if the anxiety is mild and the ADHD symptoms are the primary impairment. In certain instances, anxiety may be primary and ADHD less impairing. Additional efforts to clarify the best pharmacotherapy for this comorbid subgroup have focused on ATX.

Atomoxetine

Atomoxetine is a selective presynaptic norepinephrine reuptake inhibitor and is approved by the United States Food and Drug Administration for the treatment of pediatric ADHD/anxiety.[37] Recent research has examined efficacy for comorbid ADHD/anxiety in children and adults.[35,37-39] In 2005, researchers evaluated the effects of ATX alone or in combination with fluoxetine in the treatment of pediatric ADHD, anxiety, and depression.[38] Atomoxetine was effective for ADHD, depressive, and anxiety symptoms.[38] A similar degree of improvement was seen with ATX alone and with fluoxetine.[38] However, generalization of these results is limited due to the focus on depressive symptoms over anxiety and the absence of

a placebo arm. The percentage of children who withdrew from the study due to side effects was minimal across all groups.[38] However, the combination treatment group experienced higher increase in heart rate, blood pressure, and weight loss compared with ATX only.[38] Subsequently, in 2007, a double-blind placebo-controlled trial examined the effects of ATX for children with ADHD/anxiety.[37] Children with ADHD and generalized anxiety disorder, separation anxiety disorder, or social phobia were randomized to 12 weeks of ATX (n = 87) or placebo (n = 89).[37] Atomoxetine reduced ADHD/anxiety symptoms in children who have ADHD with comorbid anxiety.[37] Atomoxetine was well tolerated and did not worsen anxiety.[37] Sample size was not adequate to show which type of anxiety symptoms were more responsive to ATX. In adults with ADHD, social phobia symptoms responded to ATX, while generalized anxiety disorder (GAD) symptoms did not.[39] This suggests a differential effect of ATX across anxiety disorders and additional studies are needed to clarify this issue in the pediatric population. Evidence suggests that if anxiety symptoms are predominant or the patient cannot tolerate MPH, it might be reasonable to prescribe ATX to treat both anxiety and ADHD symptoms.[10] However, anxiety symptoms in some children with this comorbidity may not respond to ATX or MPH, in which case SSRIs may be considered.[10]

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors are used for the management of depression and anxiety by increasing available serotonin in the postsynaptic receptors. While SSRIs are efficacious for the treatment of mood and anxiety disorders, their benefit in the presence of ADHD with comorbid anxiety is less clear.[28] A 2004 study looked at the response of 32 children with anxiety to an SSRI after ADHD symptoms improved with MPH.[40] Children with improved ADHD symptoms but ongoing anxiety (n = 25) were randomized to either placebo + MPH or fluvoxamine + MPH for 8 weeks.[40] Fluvoxamine doses ranged from 25 to 300 mg.[40] While the combination of fluvoxamine and MPH was well tolerated, there was no group difference on measures of anxiety.[40]

Further efforts examined the effects of fluoxetine combined with ATX for children with this comorbidity.[38] Patients were randomized to ATX + fluoxetine (n = 127) or placebo + ATX (n = 46).[38] Again, there was no significant difference between the groups.[40] Of note, the number of children studied with SSRIs was small, and this research merits further examination.

As a result, guidelines regarding the use of SSRIs in these children derive largely from expert consensus, such as the Texas Children's Medication Algorithm. This guideline endorsed the use of ATX or MPH to treat comorbid ADHD/anxiety as first line.[10] If anxiety is unresponsive to these medications, SSRI initiation is recommended, especially if anxiety is severe and causing significant dysfunction.[10] Considering the potential for behavioral activation and suicidal ideation with SSRIs, close monitoring of these patients is essential.[8] In addition to medication, it is essential to address psychosocial factors to lower the symptom burden associated with this comorbidity. In many cases of moderate to severe anxiety, medication alone may not be the best approach, and psychotherapeutic options need to be considered.

Psychotherapeutic and Behavioral Interventions

The Multimodal Treatment Study of Children with Attention-Deficit Hyperactivity Disorder (MTA) is the largest study evaluating combined treatment relative to pharmacotherapy alone in children with ADHD and comorbid anxiety.[12,15,36,41] Four groups were compared: pharmacotherapy (MPH), psychosocial interventions (parent training/summer program and school adaptations), a combination of pharmacotherapy with psychosocial interventions, and usual treatment.[36] Of note, ADHD was predominantly targeted, but improvement in anxiety was also seen.[36] In fact, the MTA showed that the comorbid ADHD/anxiety subgroup had the greatest response to psychosocial treatment relative to other comorbidities.[36] In clinical practice it is difficult to reproduce the intensive behavioral package of the MTA. Nevertheless, it is widely recognized that psychosocial interventions are essential in treating these children.

In children with primary ADHD, evidence-based interventions include behavioral parent and teacher training (BPT), which teaches caregivers to use rewards and consequences to shape target behaviors.[42] Token systems and positive reinforcement (positive attention, privileges) encourage desirable behaviors, while time-out or privilege removal discourages undesirable behaviors.[15,42] For primarily anxious children, CBT is the standard treatment.[43] Cognitive behavioral therapy helps the child to recognize anxiety and develop adaptive thinking. One behavioral strategy is to develop a fear stepladder to gradually address fears and confront previously avoided situations.[43] Data indicate primary anxiety responds to CBT, even with comorbid ADHD.[44]

Of interest, a treatment manual blending BPT and CBT was created in 2012.[2] The program teaches parents strategies to reward positive behaviors and implement

punishment for disruptive behaviors.[2] It aims to improve parental confidence in ADHD symptom management.[2]

The anxiety component focuses on developing child and parent skills and approaches to cope with anxiety. The modules include education about anxiety, reframing fearful thinking, and gradual exposure to feared stimuli.[2] This program was tailored to accommodate the short attention span of these children and included the use of games, breaks, and incentives for on task behaviors.[2] In a pilot study, investigators examined the effects of this integrated program in 8 children with anxiety and ADHD.[2] The study suggests improvement in ADHD and anxiety symptoms, although only modest improvements for ADHD were seen.[2] Subsequently, 2 other small studies reported improvements in anxiety symptoms for youth with ADHD using CBT strategies.[6,45] A randomized trial in Australia evaluated CBT for children with ADHD and anxiety.[6] In this study, 12 children with ADHD and anxiety were randomized to either CBT or treatment as usual.[6] The other study examined the response of anxiety symptoms to CBT in 10 children.[45] In both studies CBT resulted in significant improvements in anxiety and ADHD symptoms, as well as in child and family quality of life.[6,45]

Psychosocial research in this population shows promising results, and this modality remains an important part of the treatment plan in improving outcomes in this population. Parents are generally receptive to psychosocial treatments, and these strategies offer the potential to improve functioning for these children and their families. One caveat is that CBT strategies may be difficult to implement with highly impulsive and inattentive children. It may also be difficult to find professionals trained to provide CBT especially in rural areas.[46] Cognitive behavioral therapy may be more effective for managing anxiety if ADHD symptoms are adequately controlled with medications.

Conclusion

Anxiety and ADHD have an elevated rate of comorbidity and a unique clinical presentation, requiring distinct diagnostic and treatment strategies. Several studies affirm the safety and efficacy of stimulants for ADHD. Despite concerns of stimulant related anxiety exacerbation, various studies endorse evidence of good tolerability when careful titration and monitoring is performed. Atomoxetine is a potential alternative to stimulants for treating comorbid ADHD and anxiety when stimulants cannot be used or are ineffective. The benefit of adding SSRIs to stimulant medications remains unclear but can be used to target residual anxiety that does not respond to MPH or ATX treatment. Psychosocial interventions are of considerable benefit in managing this comorbidity, targeting residual symptoms, and improving functioning.

In conclusion, current first-line agents for comorbid ADHD and anxiety include either MPH or ATX. When available, CBT can be used for residual anxiety and to enhance functional improvement. While further research with larger sample sizes is needed to solidify these recommendations, clinicians can feel confident that both MPH and ATX are safe and effective for this complex population.

Acknowledgments

The authors would like to thank Sophia Walker, MD (UConn Health) and Carolyn Malon, DDS (retired private practice) for their helpful comments and revision of the final manuscript. Drs. Malon and Walker have no conflicts of interest to declare.

Author Contribution

Drs. León-Barriera, Modesto-Lowe, and Ortegon contributed to the conception and design of the manuscript.
Dr. León-Barriera and Dr. Ortegon wrote the first draft of the article.
Dr. León-Barriera and Dr. Modesto-Lowe revised and wrote the final draft.
Dr. Ortegon revised the final draft.
Dr. Chaplin created the table and critically revised the final draft.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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