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A SYSTEMATIC REVIEW AND META-ANALYSIS OF β2-AGONIST MEDICATIONS TO TREAT CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): NEED FOR COMPREHENSIVE ASSESSMENT AND PHARMACOVIGILANCE

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is becoming the second leading cause of death in the world where 80% of deaths are reported from low and middle-income countries. COPD is a chronic disease of high prevalence in younger as well as older people majorly due to smoking, air pollution, long-term exposure to harmful gases, and other comorbidities. COPD with other comorbidities are frequent among patients of internal medicine part, and usually, these patients are more drug dependents. Certain COPD medications, such as β_2-agonists, antimuscarinic compounds, methylxanthines, and other combinational medicines, are considered high risk due to their involvement in ended with adverse events. Above all β_2-agonists are the first choice of medication to treat COPD. However, the efficacy of the drug is the link between the potential benefits and risks. Considering the side effects of COPD patients, it is necessary to develop appropriate drug management. Drug management is a complicated process that involves specific knowledge, techniques, and methodologies to identify risks and mitigate them with a proper action plan. Timely reporting of adverse drug reactions is required to minimize the chances of risk to patients and the

healthcare system. So, Health care professionals need to bring new practices for pharmacovigilance in COPD.

Keywords: Beta$_2$-agonists, Chronic Obstructive Pulmonary Disease (COPD), Adverse Drug Reactions (ADR), Pharmacovigilance, Nasal Patches

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic curable and preventative condition that has a high incidence in people that is characterized by prolonged respiratory system & airflow restrictions caused by airway and/or alveolar abnormalities **[1]**. It develops gradually over a period due to exposure to smoking, air pollution, occupational exposure to harmful gases, and other comorbidities like asthma from childhood & alpha-1 antitrypsin deficiency. According to a World Health Organization survey on leading causes of death in 2019, COPD was responsible for 3.23 million deaths ranking third globally. It is predicted that COPD will become the second leading cause of death in the world by the end of 2025 where 80% of deaths are reported from low- and middle-income countries **[2]**. COPD is categorized into two stages: acute exacerbation stage in which COPD patients are subjected to respiratory failure causes recurrent hospitalization & mortality and recovery stage **[3]**. As a result, minimizing the likelihood of COPD is a prior topic in the research study. The primary aims of COPD treatment are always to deliver clinical relief while reducing the risk of future exacerbations, disease progression, and death **[4]**. The drug classes commonly used to treat COPD are bronchodilators, anti-inflammatory drugs, antimuscarinics, methylxanthines, and other combination therapies.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest β_2-agonists of class bronchodilators are the first choice of medication to treat COPD **[5]**. Because of their propensity to relax airway smooth muscle, beta2-agonists are excellent bronchodilators. These β_2-agonists are classified into Short-Acting Beta Agonists (SABA), Long-Acting Beta Agonists (LABA), and Ultra Long-Acting Beta Agonists (U-LABA) based on their onset of action and duration. SABAs, as the term implies, have the shortest half-life and are used for quick symptom alleviation. Because of their longer half-life, LABAs provide prolonged, sustained therapy. Foreseen research of β_2-agonists works on the efficacy, limiting adverse events, to increase the quality of life and diminish side effects **[6]**.

However, the efficacy of the drug is the link between the potential benefits

and risks. Considering the side effects of COPD patients, it is necessary to develop appropriate drug management. Drug management is a complicated process that involves specific knowledge, techniques, and methodologies to identify risks and mitigate them with a proper action plan. Several scientific studies have been conducted to investigate the characteristics of ADRs and their reporting, particularly for life-risking and chronic disorders. These investigations are often conducted as part of clinical studies for novel medications or post-marketing studies for well-established medications. Moreover, research that investigates the severity of ADRs in chronic obstructive pulmonary disease and their relationship to therapy are uncommon, which piqued our attention **[7-9]**. Timely reporting of adverse drug reactions is required to minimize the chances of risk to patients and the healthcare system.

This article expects to provide information on the areas of concern: assessing the adverse reactions & their severity, COPD management plan, and pharmacovigilance regarding this class of medications.

PEOPLE WITH COPD AND MEDICINE RELATED VULNERABILITY

Every medication has adverse effects. However, many people do not experience the negative effects or are able to cope with them. The most prevalent side effects of beta-2 agonists involve the cardiovascular, metabolic, and/or musculoskeletal system. Because some of the β_2-adrenergic receptors in the atria and ventricles are β_2, all β_2-agonists can produce increased heart rate and palpitations. Furthermore, stimulation of β_2-adrenergic receptors can cause vasodilation and resting sinus tachycardia. The activation of β_2-adrenergic receptors in the liver causes glycogenolysis and elevates blood sugar levels. Despite simultaneous bronchodilation, β_2-agonist administration can cause a transitory drop in PaO2. Because of the activation in skeletal muscle, hypokalaemia is also a danger with β_2-agonist medication. Because hypokalaemia can cause arrhythmias, the use of β_2-agonists has been related to an increased risk of tachyarrhythmia. Dose-related tremor is one of the most common side effects of β_2-agonists, which can directly trigger β_2-adrenergic receptors on the skeletal muscle **[10-16]**. The additional side effects encountered by β_2 medicated COPD patients are anxiety, dry mouth, nervousness, vomiting, dizziness, insomnia, hypersensitivity, chest pain, respiratory tract infection.

Method

This was data-analysis research obtained from the SIDER 4.1, Scopus,

PubMed database on the adverse drug reactions and severity of a chronic obstructive pulmonary disease while using β_2-agonists such as Salbutamol, Terbutaline, Salmeterol, and Formoterol. This database includes information on approved medications and recorded ADRs with side effect frequency.

The most common adverse effects of β_2-agonists involve the musculoskeletal, cardiac and metabolic system **[20]**. β_2-agonists can cause tremor, headache, dry mouth, palpitations and cramps and are the commonest cause of adverse drug reactions **[17-18]**. The ADRs were tracked using beta2-agonists especially salbutamol, terbutaline (Short acting β_2-agonists); salmeterol, formoterol (Long acting β_2-agonists) from the SIDER 4.1 database. All pertinent data was captured in structured format. The study focused on frequently occurring ADRs to widely used COPD medications. **Figure 1** is demonstrating the ADR severity index and a total of 50 adverse drug reactions that are occurred majorly. Common presenting adverse events were tremor and headache (35%), dry mouth (30%), mood swings (27%), Palpitations (22%), excitement & nervousness (20%) and the other adverse events with least possibility are fatigue, conjunctivitis and mydriasis (1%) **[19-21, 23]**.

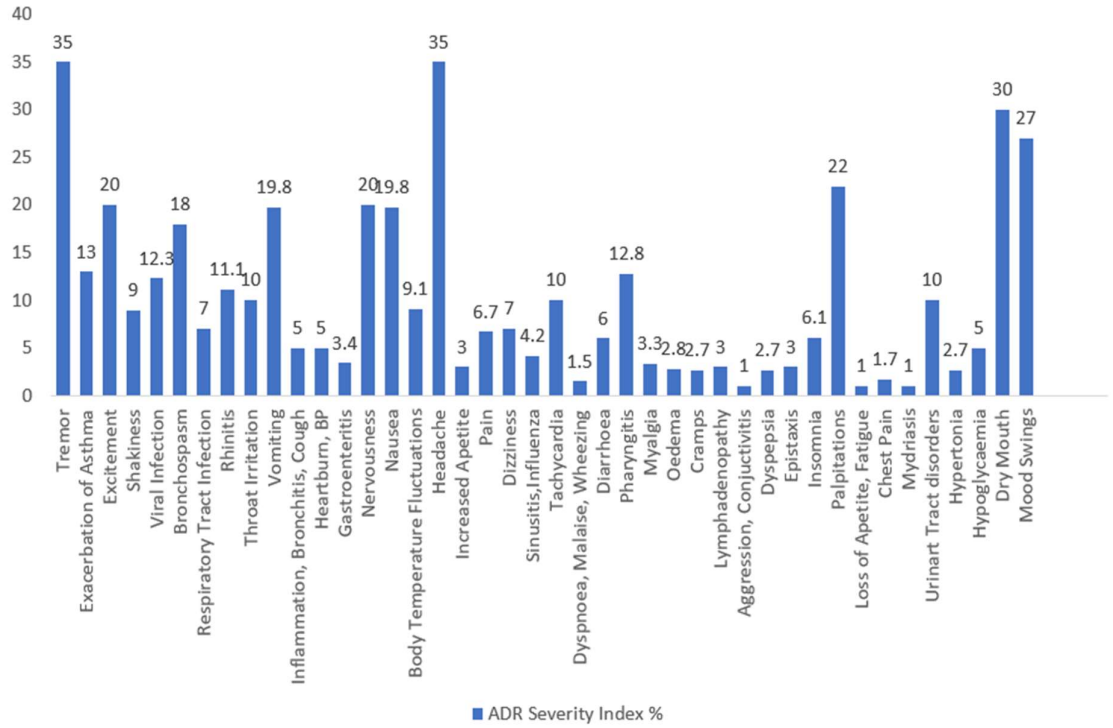

Figure 1: Beta$_2$ agonists adverse drug reactions with its ADR severity index

RESULTS

We estimating that there are more than 500 adverse drug reactions can be reported while using β_2-agonists. **Figure 1** shows the major 50 ADRs with its severity index. We selected four drug products i.e. two from short acting beta2 agonists and the other two from long acting beta2 agonists. Drug products like salbutamol & terbutaline are most commonly used medication for the treatment of COPD and these are called 'Rescue Treatment/First Line Medication' **[22-23]**. **Figure 2** is demonstrating a few major ADRs with its severity index related to salbutamol. The adverse drug reactions were tremors & headache (35%), palpitations (22%), nervousness (20%) and least possibility were increased appetite & UTI (3%) **[24-26]**.

Figure 3 is demonstrating a few major ADRs with its severity index related to terbutaline. The adverse drug reactions were tremors (38%), anxiety (31%), palpitations (29.5%) and least possibility were insomnia, dyspnoea & cramps (2%) **[27-30]**.

While coming to long acting beta$_2$ agonists, drugs like salmeterol and formoterol are majorly prescribed due to their long therapeutic action. **Figure 4** is demonstrating a few major ADRs with its severity index related to salmeterol. The adverse drug reactions were headache (20%), musculoskeletal pain (12%), hypersensitivity (10%) and least possibility were palpitations, tachycardia (2%) & hypokalaemia (1%) **[31-33]**.

Figure 5 is demonstrating a few major ADRs with its severity index related to salmeterol. The adverse drug reactions were headache (30%), viral infection (17%), palpitations (15%), and least possibility were dry mouth & insomnia (2%) **[34-35]**.

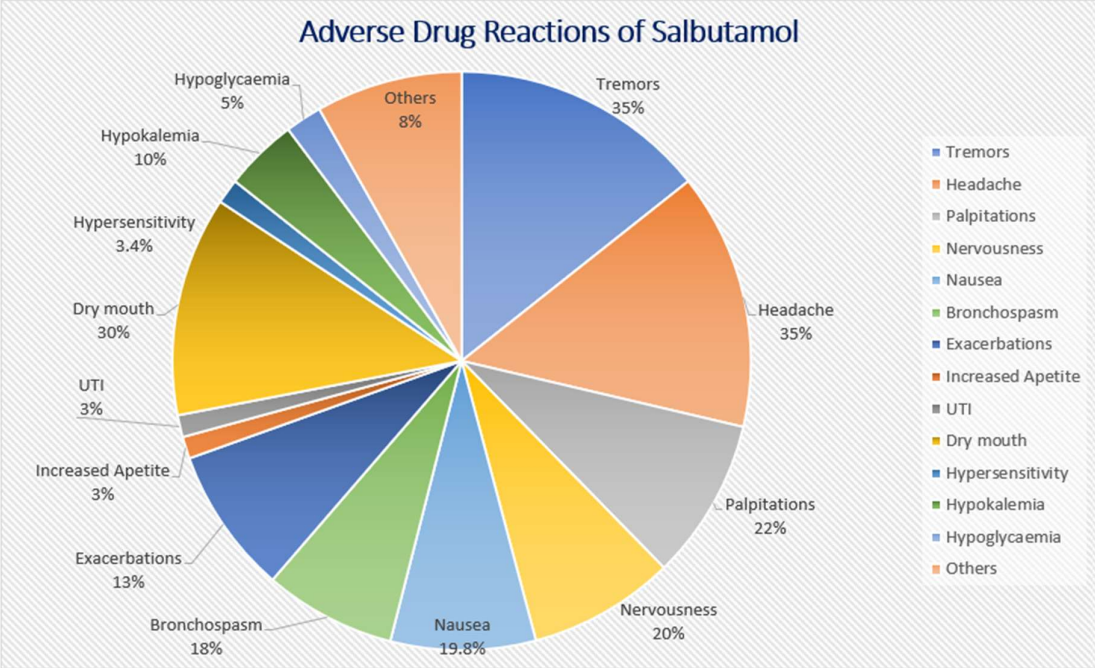

Figure 2: Pictorial representation of adverse drug reactions with its severity index of Salbutamol

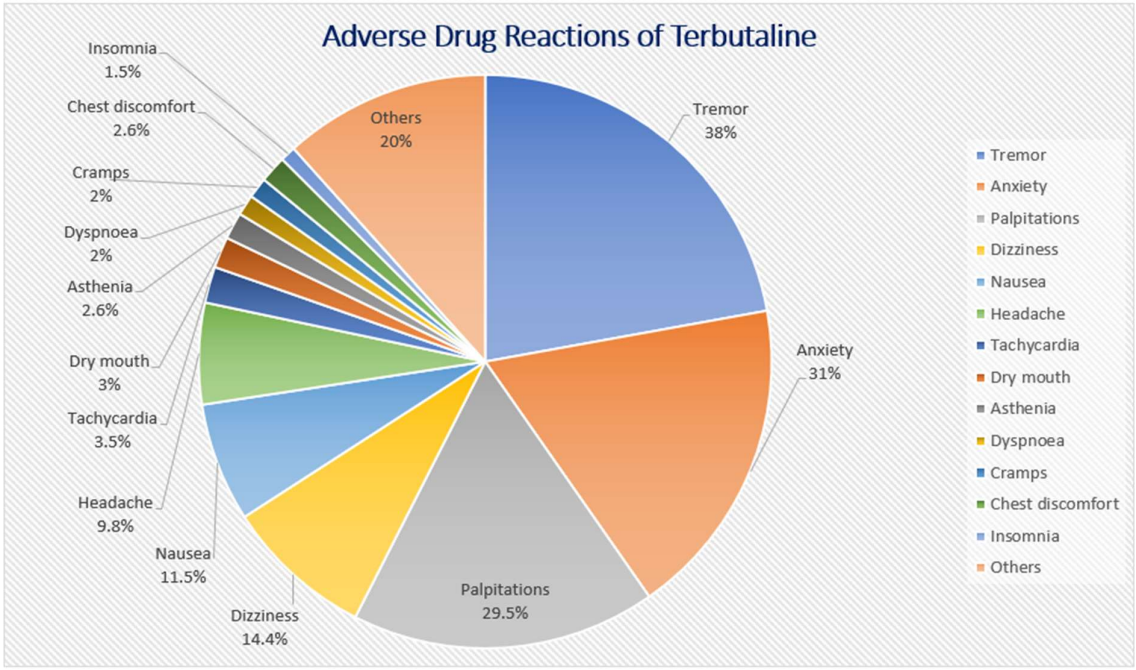

Figure 3: Pictorial representation of adverse drug reactions with its severity index of Terbutaline

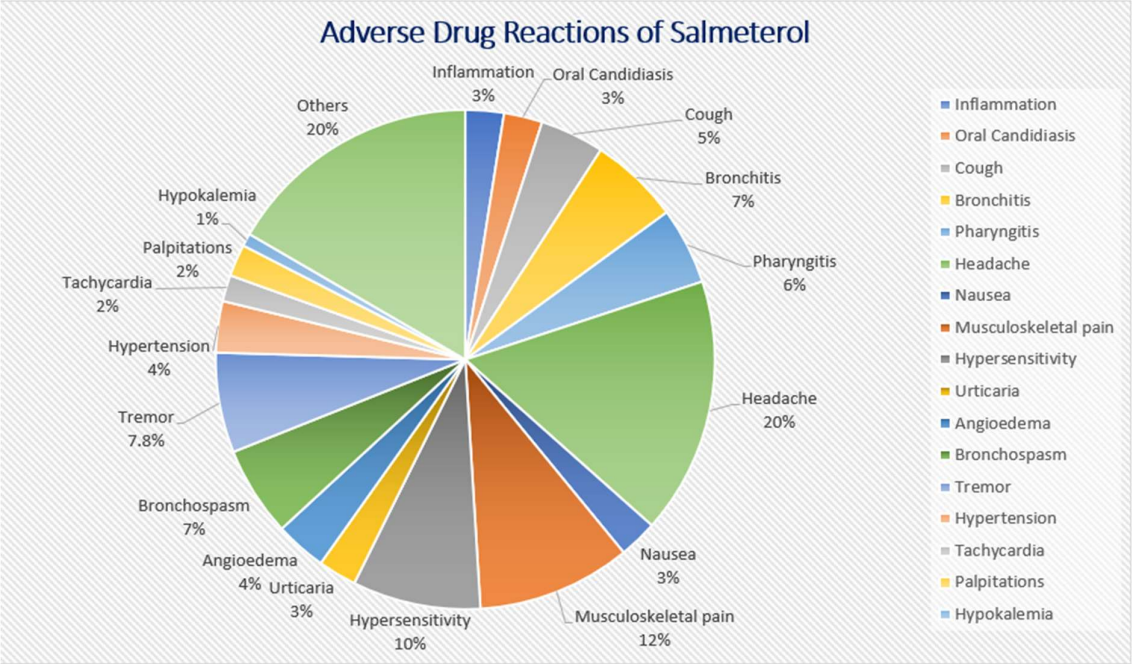

Figure 4: Pictorial representation of adverse drug reactions with its severity index of Salmeterol

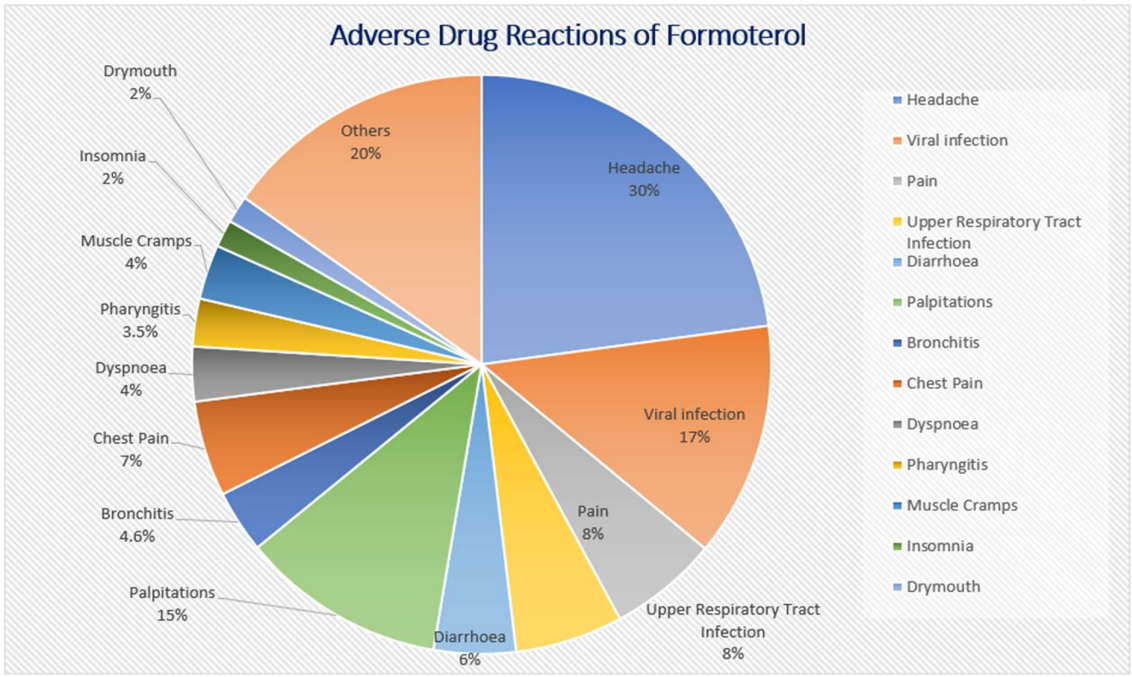

Figure 5: Pictorial representation of adverse drug reactions with its severity index of Formoterol

DISCUSSION

In this analysis we sought to describe the drug adverse effects and its severity index of $Beta_2$ agonists in COPD patients, and to determine the frequency of major drug adverse events of salbutamol, terbutaline, salmeterol and formoterol. Adverse Drug Reactions are a serious public health issue across the world, causing significant death, morbidity, and financial implications **[36]**. They can occur with any pharmaceutical medication, and hence any drug delivery mechanism is not exempt. The foundation of post-marketing drug safety surveillance, is spontaneous ADRs reporting, which is an important aspect of Pharmacovigilance. Because such monitoring happens in real-world situations, it is one of the most effective approaches for generating signals on uncommon and unexpected ADRs that were not identified in pre-marketing controlled clinical studies **[37]**.

In the study by Salpeter SR *et al*., they proved that inhaled $Beta_2$ agonists usage has risks and may be correlated to that of an upsurge in cardiovascular diseases like angina, bronchospasm **[38]**. In the study by Sangeetha P *et al*., the most common side effects of oral salbutamol were tremors (20%), palpitations (21%), and muscle cramps (18%) [39]. In the study by Petova G *et al*., a total of 84 adverse drug reactions were found on salbutamol **[40]**. In the study by Condemi JJ, the most common side effects reported were upper respiratory tract infection, viral infection, sinusitis, bronchitis, headache, rhinitis, and cough **[41]**. In Campbell's study, a total of 1171 side effects were reported during the course of the study, in which many of whom had reported more than one ADR **[42]**. In Van Schayck CP *et al*., study, it has been demonstrated that regular β_2-agonist usage increases bronchial hyperreactivity even when bronchodilation is maintained to some extent **[43-44]**. Furthermore, in the study by Cazzola M *et al*., there is a significant increase in heart rate, palpitations, and blood sugar levels; also causes decrease in arterial oxygen pressure and hypokalaemia and tremors are also noticed **[10]**.

In this study, we majorly focused on adverse drug reactions due to usage of $beta_2$ agonists and major adverse events of salbutamol, terbutaline, salmeterol and formoterol. For decades, there has been debate about the clinical safety of $beta_2$ agonists. We observed that most of the oral β_2-agonists causes tremors, headache, palpitations, damaging the respiratory tract in children's etc. As a result, a variety of aerosol devices came into market. Instead of deducing the COPD characteristics, it displays additional undesirable drug responses due to device unawareness, lack

of expertise in breathing technique, not inhaling gently, and so on. Tolerance to drug dosage is also a major concern in COPD patients, who require greater than usual doses and experience significant adverse drug reactions. We put out the notion that "Nasal Patches," which may be used to treat COPD, are really something researchers and pharmaceutical corporations ought to consider. We assume that the 'Nasal Patches' will bring a new revolution in pharma field and can save many of them from ADR's. In addition, we also suggests that appropriate signal identification, recording and reporting of adverse drug reactions is necessary.

CONCLUSION

In this study, major adverse events have been recorded with COPD medications. The common ADR's were tremors, anxiety, headache and palpitations. Beta$_2$-agonists adverse drug reactions were mostly significant when taken orally or parenterally. Additionally, there's a chance that utilising inhalers will have negative effects as mentioned in the discussion column. As a result, when a COPD patient begins and continues to use these drugs, thorough monitoring of effectiveness and safety is required. It might be suggested that more thorough monitoring of ADR appearance is required, in addition to increased reporting by healthcare professionals and patient participation on identifying and reporting ADRs. This study strongly suggests that there is a greater need for alternative drug delivery method that are safe, effective and don't have any adverse drug effects. We proposed that 'Nasal Patches' would be beneficial to COPD patients of all ages & in any condition. We assume that the 'Nasal Patches' will bring a new revolution in pharma field and might cross all the difficulties in COPD medication therapy.

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P. Vikash conducted the literature search, contributed to conceptualization, and wrote the manuscript. All authors contributed to the conceptualization, and methodology and analyzed the data. All authors reviewed and edited the manuscript. No financial disclosures were reported by the authors of this article. No conflicts of interest were reported by the authors. No copyrighted materials or tools were used for this research. This study was exempt from institutional review board approval. The findings and conclusions in this report are those of the authors.

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