

**Review Article**

# The Challenge with Salbutamol: Benefit as Treatment Modality and Detrimental Effects of Overuse

**Elmien Bronkhorst<sup>1\*</sup>, Madan Poka<sup>2</sup>**<sup>1</sup>Senior Lecturer, School of Pharmacy, Sefako Makgatho Health Sciences University, South Africa<sup>2</sup>Lecturer, School of Pharmacy, Sefako Makgatho Health Sciences University, South Africa

**\*Corresponding author:** Elmien Bronkhorst, Senior Lecturer, School of Pharmacy, Sefako Makgatho Health Sciences University, South Africa

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**Abstract**

The introduction of inhaled short-acting  $\beta_2$ -agonists revolutionized the short-term management of asthma, as it provides quick relief of bronchoconstriction. Current treatment guidelines focusing on prevention of asthma exacerbations rather than relief of acute symptoms of asthma are in place, many patients are self-medicating with short-acting  $\beta_2$ -agonists, rather than adherence to inhaled corticosteroids with long-acting  $\beta_2$ -agonists as controllers. Current treatment guidelines focusses on prevention of asthma exacerbations with the use of inhaled corticosteroids and long-acting  $\beta_2$ -agonist, rather than only using a reliever in acute symptoms. Frequent use of reliever medications are recognized as a marker of poor asthma control, and leads to increased hospitalization, morbidity and mortality.

Salbutamol is one of the most commonly prescribed SABA's as add on therapy in the treatment of asthma, but the overuse (more than 12 metered dose inhalers annually) is associated with an increased risk of severe exacerbations, including death, as well as the down-regulation of  $\beta_2$ -receptors. The availability of the medicine as an over-the-counter product can further exacerbate the problem.

Pharmacists and clinicians may play a role in determining the way the patient is using the reliever, and provide education regarding the correct use of medication, including the correct technique of using the inhaler. The aim of this review is to highlight the problem of salbutamol overuse, and to set out measures to curb the problem.

**Keywords:** Short-acting  $\beta_2$ -agonist; Uncontrolled asthma; Salbutamol; Reliever-overuse

pharmacological treatment for symptom control and minimizing risks of exacerbations [2].

Since 2006, a shift in the paradigm for asthma management has occurred, in that management now focuses on optimizing asthma control by improving current asthma symptom control and minimizing future risk, especially for exacerbations. Furthermore, it aims to reduce the loss of lung function and minimize side effects of medication used [2].

Treatment strategies still proposed using a step-wise approach (five steps) according to the medication needed to achieve control. For pharmacological management, the list of available medications has greatly increased. Although the addition of inhaled corticosteroids reduce the risk of exacerbations, and reduce the need for short-acting  $\beta_2$  agonist, [2], the SABA are still

the choice of treatment for the majority of patients [3]. Although salbutamol dependency is not a recent problem, it is of more concern when patients overuse it, since newer treatment options such as inhaled corticosteroids are relatively safe and effective [4].

Mortality and morbidity due to asthma exacerbations remain unacceptably high, despite widely disseminated guidance for asthma management. Excessive prescribing of reliever medication still exist, with around 80% of patients provided with reliever medication, of more than 12 reliever inhalers in a year, without adding a preventer medication. At the time of death, 3% of patients were on long-acting  $\beta_2$ -agonist (LABA) monotherapy [3]. Frequent overuse of SABA is internationally recognized as a marker of poor asthma control, hospital admissions for severe exacerbations and even Intensive Care Unit admission [5,6].

### **Clinical Indications, Dose and Mechanism of Action**

Salbutamol is a short-acting sympathomimetic  $\beta_2$ -selective adrenoceptor agonist, which produces a rapid onset (10-15 minutes) of bronchodilator effect [7,8]. It is used in the treatment of acute and severe bronchospasm caused by asthma exacerbations, prophylactically in acute exercise-induced bronchospasm, to relieve the symptoms of bronchospasm associated with other reversible airways obstructive disorders such as bronchial asthma and bronchitis in both children and adults [8,9].

Each dose of the salbutamol metered-dose inhaler-device contains 100 micrograms of salbutamol, together with a propellant. The prescribed dose for salbutamol inhalation is 1-2 puffs every 4-6 hours as needed, for the relief of bronchoconstriction. To use as prophylaxis for exercise-induced bronchoconstriction, use 1-2 puffs 15minutes before exercise [1].

The mechanism of action of salbutamol is well established. It acts by relaxing the smooth muscles of the airway through a series of intracellular events. Briefly, the activation of  $\beta_2$  receptors in the bronchial smooth muscles results in the activation of adenylyl cyclase enzyme, causing increased levels of cyclic adenosine 3', 5'-monophosphate (cAMP), which in turn results in the physiologic effect due to decreased concentration of intracellular calcium ions [9,11]. When administered through oral and intravenous routes, along with the bronchodilator effect, it also exhibits dose dependent positive inotropic and chronotropic effects in cardiac muscles, resulting in sinus tachycardia [12,13]. Additionally, it is used as an adjuvant in the emergency treatment of hyperkalemia [14].

Salbutamol is one of the most commonly prescribed SABA's as add on therapy in the treatment of asthma [15]. The Global Initiative for Asthma Management (GINA) guidelines, indicate that the SABA's are no longer recommended as monotherapy in the treatment of acute condition of asthma, rather used for a very short period to improve the symptoms during an acute attack. In the management of asthma, salbutamol plays a role of "Reliever/Rescue medication" to use when required rather on a regular basis [16].

### **Overuse of Salbutamol**

Short-acting  $\beta_2$ -agonist overuse is defined as 12 prescriptions/ dispensations or more inhalers over a 12 month period, or prolonged use of more than four doses (eight puffs) per day [3]. Observational studies have reported the overuse of  $\beta$ -agonist drugs is associated with an increased risk of severe exacerbations, including death [5]. In the 1980's, overuse of SABA's was associated with an epidemic of asthma deaths, and the dispensing of more than 12 inhalers per annum was directly associated with increased risk of asthma-related death. Despite developing and introducing guidelines for the management of asthma, a significant proportion of patients living with asthma still rely, to their detriment, on SABA as their sole asthma treatment [1].

Factors that could potentially contribute to patient use of reliever-only treatment could be the ease with which it can be obtained. The inhalers are also relatively cost-effective, when compared to preventer inhalers like inhaled corticosteroids. Users of frequent SABA reported having them everywhere, and that they become "panicky" if they do not have the inhaler readily available. They will typically have more than one SABA inhaler available at different sites, (work, handbag, car, house). SABA-inhalers figured prominently in their thinking about asthma, providing a quick fix and a tool to enable them to get on with their busy lives. Patients feel that the convenience of a single inhaler is preferable above carrying more than one inhaler. Furthermore, the SABA provides quick relief and is cheap, while the inhaled corticosteroids do not stop wheezing and coughing immediately and are considerably more expensive [6].

The Food and Drug Administration (FDA) in the United States still did not approved the Over The Counter (OTC) sale of SABA, although the debate on the benefits are ongoing. However, in Australia it has been available as an OTC product for more than 30 years [1], and in South Africa, salbutamol has a S<sub>2</sub> status, and has been available as OTC product for many years. A recent study performed in South Africa, found a high utilization of bronchodilators, possibly indicative of poor control of respiratory conditions [17]. The safety aspect of this practice are concerning, since no population-based data have been available to provide evidence of the safety of supplying SABA without a prescription [1].

The magnitude of the impact of inappropriate reliever-only treatment are difficult to assess, as clinicians are often unaware of the OTC purchases of relievers, and the lack of filling of preventer prescriptions [1]. Over the counter supply of SABA has been linked to under treatment of asthma and medications are often used by patients without regular medical supervision [18].

### **Effects of Salbutamol Overuse**

The mechanism of salbutamol toxicity includes stimulation of  $\beta_2$ -receptors, which will result in relaxation of smooth muscles in the bronchi, uterus and skeletal muscle vessels. At high doses, which will happen with overuse of SABA, selectivity for  $\beta_2$ -

receptors may be lost, and  $\beta 1$  effects can be seen, including vasodilation, tachycardia, myocardial ischemia and infarction, agitation and muscle tremors and metabolic effects [19].

Although only a few reports of inhaled salbutamol overuse are available, given the ubiquitous use of salbutamol, many patients may experience symptoms of overdose on a spectrum that ranges from mild side effects to severe toxicity. Often patients will report using the salbutamol inhaler more than once (sometimes up to 15 times) during an “acute asthma attack”. Physical examination of such patients will reveal severe agitation. Cardiac examination can reveal fast rhythm and sinus tachycardia. Blood gas results may reveal respiratory alkalosis with metabolic acidosis and increased lactate. Low potassium levels, can be expected [20].

Long term use of salbutamol can lead to down regulation of the  $\beta_2$ -adrenoceptors. This is attributed to changes in protein transcription or translation, changes in receptor cellular location, prolonged phosphorylation leading to endocytosis of the receptor [11]. The down regulation of the receptors further results in the release of pro-inflammatory cytokines. *In vitro* studies conducted by Oheme, et al. [2], established a time and concentration dependent down regulation of  $\beta_2$ -adrenoceptor receptors, leading to the release inflammatory mediators, Interleukins (IL) IL-6 and IL-8.

Long term and excessive use of SABA's (use of more than one canister per month) can result in worsening of asthma, poor quality of life (both physically and mentally), increased emergency admissions, higher health care costs and increased chances of mortality [16,22,23]. Not much research has been done to date to understand the reasons for abuse of salbutamol. Research conducted by (Boyd 2008; Pratt 1983) [24,25] among school students and adolescents respectively indicated the high prevalence for use of salbutamol in the management of asthma. Effects of overuse such as convulsions, diminished bronchodilator response, possible effects of intoxication and reduced anxiety associated with the wheezing sound, were observed.

## Possible Interventions to Curb Overuse

### Managing triggers

Excessive use of salbutamol inhalers, mainly results from the poor management of the disease condition leading to frequent recurrence of the exacerbations [26]. Constant exposure to varying “triggering factors”, leading to inflammation and constriction of the airway [27,28], need to be addressed with non-pharmacological interventions and life-style modification, to break the cycle of salbutamol dependency. Simple interventions such as regular and controlled exercise, use of face masks to avoid exposure to triggers, focused breathing to control stress and anxiety, are proven for their efficacy in reducing the asthma attacks [29,30].

### Improve adherence

Sub-optimal adherence (around 50%) among adults and very poor among child population (around 30%) is identified [31,32],

which can be attributed to barriers such as low-socioeconomic status, health literacy, high cost, access to health care, language, fear of stigmatization, side effects, improper inhaler technique and complacency [32,33]. Adherence to the prescribed treatment plays a vital role in controlling the daytime symptoms, exacerbations and acute asthma attacks [28], leading to less frequent requirement of reliever medications. One of the most effective approaches is communication between the physician and patient. Studies found that patients were highly appreciative of the physicians taking time to explain the disease state and management, rather than simply prescribing medication. Lack of communication, resulting in lack of knowledge has a profound negative impact on the adherence [34]. Techniques such as subjective monitoring questionnaires, objective monitoring through counting the doses left, direct observations by family members and social workers, use of electronic monitoring and reminder systems that are linked to smart phones were recommended to improve the adherence [35]. However, improving the adherence needs customized approaches based upon the underlying barriers.

### Review visits

The 2021 GINA guidelines recommends that the patients should be seen 2 - 4 weeks for step-down, 2-3 months for step-up treatment and every 3-12 months for maintenance [16]. Attending the planned review visits improved the clinical outcomes significantly with reduced exacerbations [36]. These visits can be used to review the medication and either step-up or step-down the dose, assess the inhaler technique and improve adherence through education.

### Patient education

Patient education has been an important intervention in managing several diseases conditions, along with asthma. Educating patients during their regular visits plays a vital role in translating the benefits of above-mentioned interventions (handling of triggering factors, adherence, following the set treatment plan) into desired therapeutic outcomes. Education equips patients with necessary knowledge and skills (inhaler technique) in the self-management of the condition and improve negative behavior [37], such as repeated use of relievers. Educating adolescents with such chronic illness is particularly important to allow a smooth transition into responsible adults. Continuous efforts to educate adolescents will assist in alleviating stigma to use the inhaler, depression and frustrations over inability to take part in certain activities, and anxiety associated with relying on someone during an attack [38]. All the stakeholders of the health care system (Physician, nurse and pharmacist) play a vital role in educating patients to emphasize the importance of using regular preventer therapy, handling of side effects and importance of adherence despite the lack of symptoms.

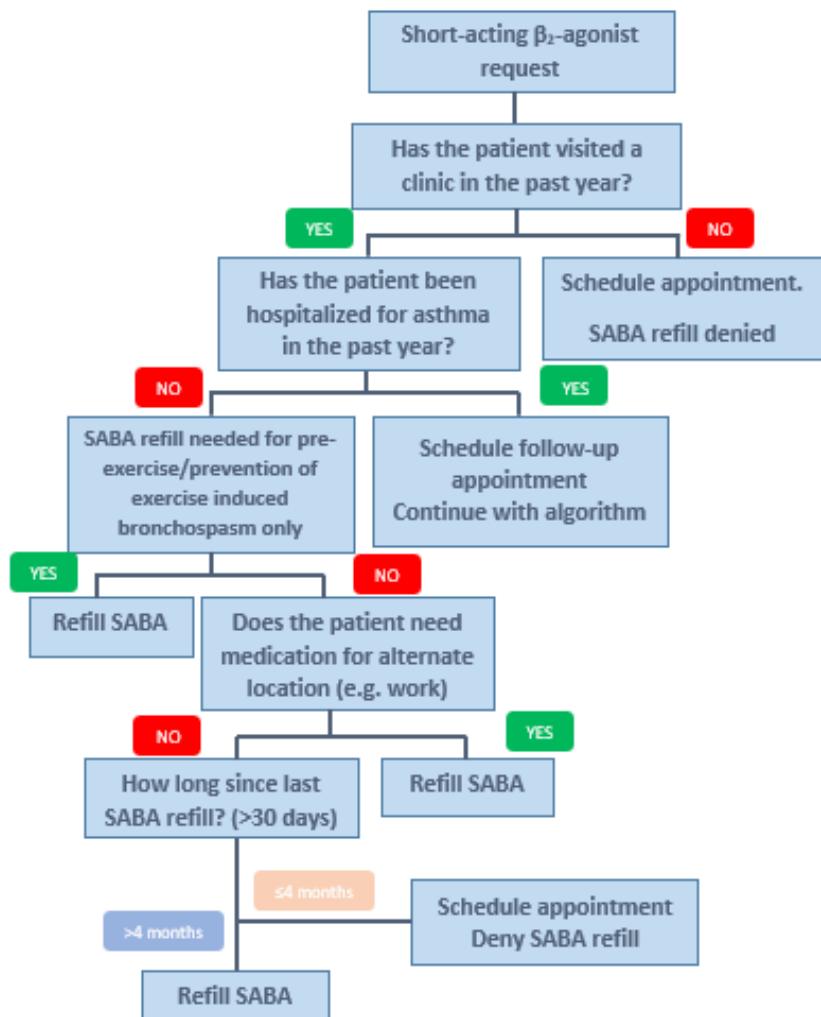
### Scheduling status

In South Africa, salbutamol inhalers are available as OTC medication and they are relatively cheap in comparison with the controller medication. In countries such as United States

of America (USA), Canada and United Kingdom (UK), it is categorized as prescription only medicine (Information is obtained from the recent patient information leaflets). There is paucity of studies that can provide a correlation between the free availability of salbutamol inhaler versus dependence. The 2015 Asthma Insight and Management Survey conducted across the regions of Asia-Pacific, Latin America, Europe, Canada, and the United States noted a staggering 60% of the patients using salbutamol on a daily basis. The dependency is mostly related to lack of knowledge and attitude of the patients towards the controller treatment [39]. Change in the schedule status of the salbutamol inhalers to a higher schedule might address the current situation to some extent. However, the benefits of such intervention highly depend on the prescribing patterns, including refill quantities in patients receiving more than one refill per month [40].

## The Role of the Pharmacist in Reducing Overuse

Pharmacists can play a role in effective asthma control by determining the frequency of SABA use, as well as determining the symptoms like frequency of daytime symptoms, frequency of nighttime symptoms, level of activity interference, exacerbations per year and emergency department visits because of asthma. Regarding the medication use, the pharmacist may determine the quantity of inhalations taken with each administration, as well as if the patient are using controller medication, and their adherence to controller medication. After determining the patient's relationship with the asthma treatment plan, education may be provided regarding the correct use of medication, as well as the correct technique for using the inhalers [41]. Figure 1 depicts a proposed algorithm for the pharmacist to identify reliever overuse.



**Figure 1:** Proposed algorithm to identify reliever overuse [41].

An important role for the pharmacist is to identify non-adherence to controller medications, or inhaled corticosteroids. [39]. Non-adherence can be suspected when the patient are using the controller medication less than 80% of the time. Furthermore, pharmacists can also encourage continuous long-term health management, by suggesting smoking cessation, healthy lifestyle and ensuring patient care follow-up to clinics or primary prescribers [41].

## Conclusion

Salbutamol is still the most commonly prescribed medicine to relieve the symptoms of bronchoconstriction in asthma. However, the overuse of  $\beta$ -agonist drugs is associated with an increased risk of severe exacerbations, including death. Salbutamol is available as an over-the-counter medicine, which further exacerbates the problem of overuse. Because of this reason, clinicians are often unaware of the extent of the problem, and most patients overusing the relievers, have poorly controlled asthma. Pharmacists may play an important role in identifying patients that overuse the relievers, and may provide them with necessary information, or refer them to clinics or primary prescribers for proper management of asthma symptoms.

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