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REVIEW

Adverse events of clenbuterol among athletes: a systematic review of case reports and case series

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Abstract

Clenbuterol is a potent beta-2 agonist widely misused by professional athletes and bodybuilders. Information on clenbuterol associated adverse events is present in case reports and case series, though it may not be readily available. This systematic review aimed to critically evaluate the evidence of adverse events associated with clenbuterol among athletes. The search strategy was in accordance with PRISMA guidelines. Databases such as PubMed, Science Direct, Scopus, and Google Scholar were searched from 1990 to October 2021 to find out the relevant case reports and case series. There were 23 included studies. Using a suitable scale, the included studies' methodological quality analysis was evaluated. In total, 24 athletes experienced adverse events. Oral ingestion of clenbuterol was the most preferred route among them. The daily administered dose of clenbuterol was ranging from 20 µg to 30 mg. Major adverse events experienced by athletes were supraventricular tachycardia, atrial fibrillation, hypotension, chest pain, myocardial injury, myocarditis, myocardial ischemia, myocardial infarction, cardiomyopathy, hepatomegaly, hyperglycemia, and death. The cardiac-related complications were the most commonly occurring adverse events. Clenbuterol is notorious to produce life-threatening adverse events including death. Lack of evidence regarding the performance-enhancing effects of clenbuterol combined with its serious toxicities questions the usefulness of this drug in athletes.

Keywords Clenbuterol · Bodybuilding · Athletes · Adverse events · Adverse effect

Introduction

Clenbuterol is a potent sympathomimetic drug that acts by binding with beta-2 adrenergic receptor. It has higher potency compared to other approved beta-2 agonists like salmeterol [1]. In addition to beta-2 selectivity, it also has an affinity to bind with beta 1 and beta 3 adrenoreceptor [2]. It induces lipolysis and weight loss by binding to the beta 3 adrenergic receptor of adipocytes [2]. The drug has a long half-life and is quickly absorbed from the gastrointestinal tract. The detailed pharmacokinetic parameters of clenbuterol when administered a single dose of 40 µg orally are presented in Table 1 [3].

It is available in different dosage forms including tablet, syrup, injectable, and aerosol. In many countries, this drug is prescribed for the treatment of acute exacerbation of asthma with a recommended dose of 20 to 40 µg, twice daily [4, 5]. Apart from human use, it is widely used in the respiratory disorder of horses and postponing parturition in cows [6]. Clenbuterol is one of the highly abused drugs among bodybuilders and young fitness fanatics for the development of lean muscle and losing body fat [7]. Numerous studies of clenbuterol are associated with serious adverse reactions [8–10]. In addition, it is also used by athletes to improve performance due to its anabolic effects. Hence, World Anti-Doping Agency (WADA) and International Olympic Committee banned this agent and included it in the list of prohibited substances [11]. The US-FDA and the European Union also prohibited this drug for administration to any animals that are used as food by humans [12]. However, the interesting and unfortunate part is that clenbuterol is easily available on the internet and promoted by

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Table 1 Pharmacokinetic parameters of clenbuterol

Pharmacokinetic parameters	Normal range of clenbuterol
Absorption	Fast absorption through GIT
Bioavailability (orally)	89–98%
Tmax	2–3 h
Protein binding	89–98% (administered dose, 80 µg/man)
Excretion (renal)	20% excreted unchanged
Plasma half-life	35 h

advertisers for muscle building, weight loss, lipolytic, dietary supplement, metabolic, and performance enhancer [13]. It was found to be adulterated with heroin and cocaine [14].

This drug is used alone or in combination with anabolic steroids, growth hormones, protein supplements, synthetic thyroid hormone, insulin, and many others [5, 8, 9]. Clenbuterol at a normal dose is reported to produce toxicities such as rhabdomyolysis, myocarditis, fever, tachycardia, thirstiness, diaphoresis, and shortness of breath [5, 15, 16]. Sympathomimetic features associated with clenbuterol toxicity include restlessness, tremor, palpitation, tachycardia, gastrointestinal problem, and metabolic abnormalities such as hyperglycemia and hypokalemia [17]. Clenbuterol, even at a low dose (20 µg), reported producing adverse effects such as palpitation, chest pain, tachycardia, hyperglycemia, and electrolyte imbalance [10]. Similar toxicities have also been reported in animal studies. Impairment of liver function was observed after administration of a growth-promoting dose of clenbuterol in pigs [18]. Significant necrosis of skeletal and cardiac muscle has been reported after administration of clenbuterol in rats [18]. It also exhibits structural and functional impairment of trypsin an important enzyme that assists in digestion [19].

Despite all these serious adverse events to date, no systematic review was performed on clenbuterol highlighting toxicities. Therefore, we aimed to perform a systematic review to identify and critically appraise all the case reports and case series studies on clenbuterol and associated adverse events. This study will be helpful to health care professionals to educate bodybuilders/gym-goers, athletes, trainers, teenagers, and their parents to refrain from the use of this doping agent. Furthermore, it will also be helpful for authorities to take appropriate measures to prevent the illegal marketing of this medicine.

Methodology

Search strategy and study selection

Several reliable scientific databases, including PubMed, Science Direct, Scopus, and Google Scholar, were used to conduct a systematic search. The search was performed according to the Boolean information retrieval method [20]. The following keywords were used: clenbuterol, bodybuilding, bodybuilder, gym, fitness center, sports, athletes, adverse effects, safety, adverse events, adverse drug reaction, side effect, toxicity, and abuse. Boolean operators ("OR," "AND") were used to identify the potential articles and records that fulfill our research outcome. We also searched the bibliographies of all included studies to find additional studies that could be incorporated into our review.

Only case reports and case series studies that reported adverse events after administration of clenbuterol by athletes and articles published in English were included. We only included case reports and case series studies where full-text article was available. Articles published from 1990 to October 2021 were considered in this review. The title and abstract of all the studies were screened for relevancy. For potentially illegible studies, the full text was obtained and independently assessed for relevance by two investigators (SK and BP). In case of disagreement between reviewers over the eligibility of studies, a senior reviewer (DT) was consulted to reach a consensus. A comprehensive flow chart for the selection of study is depicted in Fig. 1.

Methodological quality assessment

The level of evidence in included studies was categorized using Oxford Centre for Evidence-based Medicine Level of Evidence (2011) [21]. In which, level of evidence was graded as follows: a review of randomized controlled trials was 1, randomized controlled trial 2, nonrandomized controlled cohort study as 3; case-series as 4, case–control studies, or historically controlled studies; and mechanism-based reasoning defined as levels 5. Two independent examiners assessed the methodological quality of the included study by using the scale developed by Murad et al. for-case reports and case series [22]. It consisted of 8 questions that provided a quality score. These questions are categorized into 4 domains, for instance, selection (question 1), ascertainment (questions 2–3), causality (questions 4–7), and reporting (question 8). A total of 8 scores is used for quality assessment, a score of 6–8 is considered as good, 3–5 as moderate, and a score below 3 as poor-quality evidence. In case of disagreement on the score, the senior investigator (DT) was consulted to conclude.

Data collection

Two investigators (SK and BP) extracted the relevant data independently from standardized data collection sheets created in Microsoft Excel after consensus among all investigators. For studies fulfilling the eligibility criteria, data were extracted on (1) first author name, (2) year of publication,

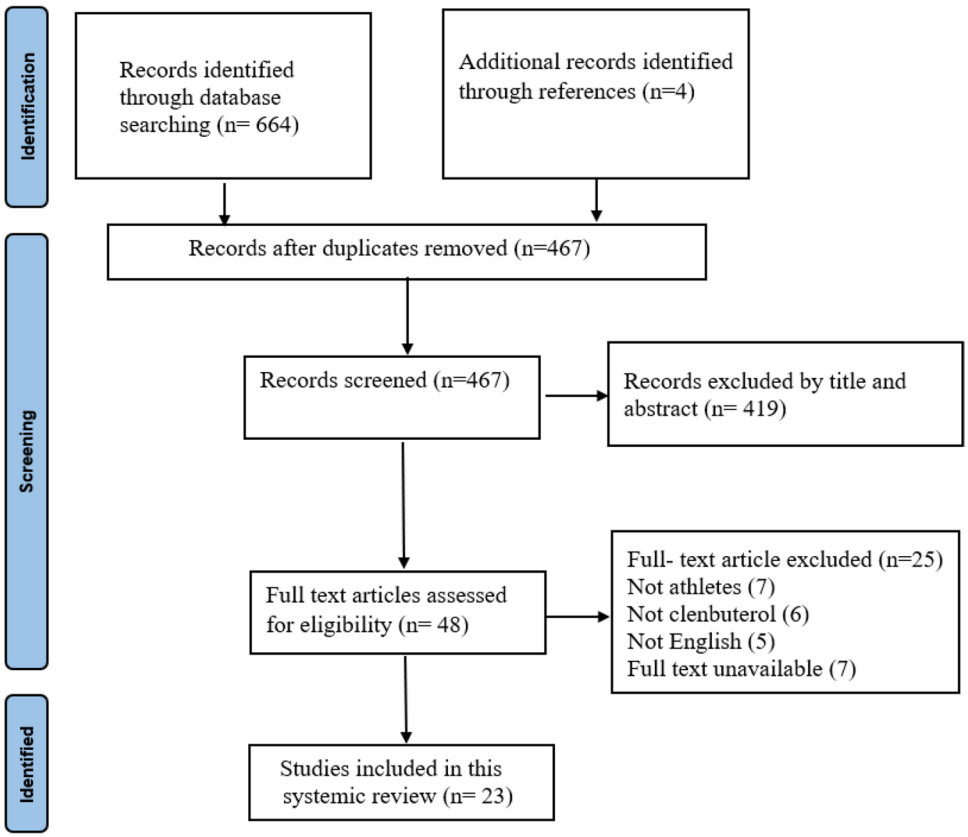

Fig. 1 PRISMA flow diagram for the selection of studies [81]

(3) study place, (4) study design, (5) patient demography, (6) total number of cases reported in the study, (7) administered dose of clenbuterol, (8) route of administration, (9) duration of use, (10) adverse event, and (11) concomitant therapy.

Results

Level of evidence and quality assessment

As per the Oxford 2011 criteria, the level of evidence for the case series was graded as 4, and the remaining were considered as 5. The methodological quality score of the included study revealed 18% studies ($n=4$) rated as good, 64% ($n=14$) as moderate, and 18% ($n=4$) as low. A detailed overview of the studies is presented in Table 2.

Study characteristics

This review included 23 papers, 22 of which were case reports and 1 case series study. The total number of athletes who develops adverse events to clenbuterol were 23. The included studies were originated from the USA, Germany, UK, France, China, Turkey, Poland, Israel, Portugal, Slovenia, Switzerland, Ireland, and Italy. Seventeen studies were published between 2010 and 2021, four studies between 2000 and 2010, and two studies in the year 1998.

Six studies reported adverse events due to clenbuterol monotherapy and the remaining seventeen studies reported polypharmacy with other performance-enhancing drugs. Various drugs concomitantly used with clenbuterol were anabolic steroids, tamoxifen, insulin, thyroid hormone, human growth hormone, human chorionic gonadotropin, diuretic, 2,4-dinitro-phenol, ephedrine, clomiphene, anastrozole, zinc, protein, and multivitamin. Oral ingestion of clenbuterol was the most preferred route among athletes. A total of 11 studies reported oral administration of clenbuterol, 1 study reported parenteral, and the remaining studies had no information on the route of administration. The clenbuterol was used at a dose ranging from 20 μg to 30 mg daily. The age of study participants varied from 17 to 61 years. Apart from 1 case, all athletes were male.

AEs after taking clenbuterol included anxiety, palpitations, shortness of breath, agitation, fever, thirstiness, diaphoresis, tachycardia, supraventricular tachycardia and atrial fibrillation, hypotension, chest pain, myocardial injury, myocarditis, myocardial ischemia, myocardial infarction, cardiomyopathy, raised lactate and troponin, deranged liver function, acute hepatic injury, hepatomegaly, hepatic rupture, rhabdomyolysis, acute renal failure, end-stage renal disease, hyperglycemia, hypokalemia, hypophosphatemia,

Table 2 Methodological quality assessment of studies included

First author (Ref.)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Assessment
Hausmann [42]	×	√	√	×	×	×	√	√	Moderate
Goldstein [37]	×	√	√	√	×	×	√	√	Moderate
Roger [51]	√	√	√	√	×	×	√	√	Good
Kierzkowska [25]	×	×	√	√	×	×	√	√	Moderate
Daubert [8]	√	√	√	√	×	×	√	√	Good
Young [9]	×	×	√	×	×	×	√	√	Low
Huckin [33]	×	×	√	√	×	×	√	√	Moderate
Perera [82]	×	√	√	×	×	×	√	√	Moderate
Grimmer [5]	√	×	√	√	×	×	√	√	Moderate
Santos [32]	×	×	√	×	×	×	√	√	Low
Michael [10]	×	×	√	√	×	×	√	√	Moderate
Mayer [83]	×	×	√	×	×	×	√	√	Low
Matthew [43]	√	√	√	√	×	×	√	√	Good
Mascagni [49]	√	×	√	×	×	×	√	√	Moderate
Zlek [84]	×	√	√	√	×	×	√	√	Moderate
Cheng [85]	×	×	√	×	×	×	√	√	Low
Lehmann [41]	√	√	√	×	×	×	√	√	Moderate
Asher [86]	×	×	√	√	×	×	√	√	Moderate
Kintz [40]	√	√	√	√	×	×	√	√	Good
Linda [30]	×	×	√	√	×	×	√	√	Moderate
Dufayet [52]	×	√	√	×	×	×	√	√	Moderate
Natassaja [15]	×	×	√	√	×	×	√	√	Moderate
Bonnar [31]	×	√	√	√	×	×	√	√	Moderate

hypomagnesemia, thyrotoxicosis, severe rhinovirus pneumonia, and death.

The AEs after taking clenbuterol alone were myocardial infarction (MI), myocarditis, myocardial injury, hypokalemia, tachycardia, hypophosphatemia, hyperglycemia, and raised lactate and troponin. Cardiac complications such as MI, myocardial ischemia, myocarditis, and arrhythmia were the commonly occurring adverse events. A total of 5 cases of death were reported. A detailed summary of study characteristics and reported AEs are presented in Table 3.

Discussion

The present systematic review aimed to critically evaluate the available evidence from case reports and case series studies of adverse events due to clenbuterol among athletes. After a thorough search of the literature, 23 articles that met the eligibility criteria were included. Adverse events of clenbuterol are like those associated with another β2 adrenergic agonist that includes palpitations, tremors, anxiety, agitation, nausea, and vomiting are typical. The finding from our review suggests that clenbuterol may lead to serious toxicities that outweigh any benefit for sports or bodybuilding competition.

In Italy and Germany, clenbuterol is approved for the treatment of asthma and COPD in humans with the prescribed dose range of 20–40 µg/day [23, 24]. In this study, many athletes used high dose [dose range 20 µg–30 mg/daily] of clenbuterol than recommended for human use in respiratory disorders. Clenbuterol used by athletes was as high as 30 mg/day which is almost 1000 times higher than recommended for human use [25]. Along with polypharmacy, the use of high dose clenbuterol could be the reason for serious toxicities among athletes. Toxicity was developed even at normal dose (20 µg) in an athlete too [10]. This indicates that it can produce toxicities even at a normal dose in sensitive users. In countries like China, Mexico, Portugal, and Italy, clenbuterol has been used as a growth promoter in animal production. Consequently, edible meat was shown to be tainted with clenbuterol residues, which can increase the risk of toxicities and adverse analytical findings in athletes. Numerous cases of clenbuterol toxicities following the eating of meat have been reported from different parts of the world. Symptoms can include nausea, vomiting, headache, dizziness, distal tremors, fever, diarrhea, abdominal, pain, hypertension, hypokalemia, leucocytosis, dry mouth, and hyperglycemia [26, 27].

A detailed analysis of various AEs is presented here.

Table 3 Summary of AEs of clenbuterol

Author (year) country (Ref)	Study design	Sample size/ patient(s) description	Dose/frequency of clenbuterol	ROA	Duration of use	Analytical findings	Concomitant therapies, dose	Adverse event
Clenbuterol monotherapy								
Kierzkowska et al. (2005) Poland [25]	CR	1/17-year-old male	40 µg/daily	Oral	NM	NM	None	MI
Huckins et al. (2013) USA [33]	CS	1/18-year-old male 1/22-year-old male	NM/NM 30 mg/NM	NM	NM	NM	None	Myocardial ischemia tachycardia
Michael et al. (2016) UK [10]	CR	1/25-year-old male	20 µg/day	Oral	3 weeks	NM	None	Hypokalemia, tachycardia, hypophosphatemia, hyperglycemia, and raised lactate and troponin
Asher et al. (2019) Israel [86]	CR	1/33-year-old Male	120 µg/NM	Oral	NM	NM	None	Myocardial injury
Linda et al. (2019) USA [30]	CS	1/22-year-old male	NM/NM	NM	2 weeks	NM	None	MI
Natassaja et al. (2020) UK [15]	CR	1/22-year-old male	40 µg/NM	NM	1 week	NM	None	Myocarditis
Clenbuterol combination with other drugs								
Hausmann et al. (1998) Germany [42]	CR	1/23-year-old male	0.02 mg/NM	Oral	9 months	NM	Testosterone cyclopentilpropionate, 250 mg Methenolone enanthate, 100 mg Mesterolone, 25 mg Liothyronine hydrochloride,100 µg Spironolactone, 100 mg Clomiphene, 25 mg	Death
Goldstein et al. (1998) USA [37]	CR	1/26-year-old male	NM/NM	Oral	NM	NM	Methandrostenolone, NM Stanozolol, NM Testosterone, NM	MI
Roger et al. (2001) Germany [51]	CR	1/27-year-old male	NM/NM	Oral	1.6 years	NM	High-protein diet, 2 gm/kg/day Testosterone, 750–1000 mg/week	End stage renal disease
Daubert, et al. (2007) USA [8]	CR	1/31-year-old male	109 µg/day	Oral	30 min	NM	Tamoxifen, NM Flax seed oil, NM Taurine, NM Multivitamin, NM	Anxiety, palpitations, shortness of breath, supraventricular tachycardia, and atrial fibrillation

Table 3 (continued)

Author (year) country (Ref)	Study design	Sample size/ patient(s) description	Dose/frequency of clenbuterol	ROA	Duration of use	Analytical findings	Concomitant therapies, dose	Adverse event
Young, et al. (2007) UK [9]	CR	1/36-year-old male	240 µg/day	NM	NM	NM	Growth hormone, 4 IU/ day Insulin, 8 IU/day Testosterone propionate, 1000 mg/week Deca durabolin 800 mg /week Oxymetholone, 100 mg/ day Methandrostenolone 100 mg/day Testosterone enanthate, 1000 & 800 mg/week T3, 50–200 µg /day Boldenone undecylenate, 600 mg/week Fluoxymesterone, 20 mg/day Mesterolone, 100 mg/ day Anastrozole, 1 mg/day Stanozolol, 10 mg/day Trenbolone acetate, 100 mg/day Spironolactone, 10 mg/ day hCG, 2500 IU thrice weekly	Deranged liver function hepatomegaly, acute renal failure, hyperglycemia

Table 3 (continued)

Author (year) country (Ref)	Study design	Sample size/ patient(s) description	Dose/frequency of clenbuterol	ROA	Duration of use	Analytical findings	Concomitant therapies, dose	Adverse event
Perera et al. (2013) USA [82]	CR	1/35-year-old male	NM/NM	Oral	> 10 years	NM	Testosterone enanthate, NM Testosterone propionate, NM Nandrolone decanoate, NM IGF-1, NM, Hgh, NM Tamoxifen, NM hCG, NM T4, NM Protein and amino acid supplement, NM Vitamin-C, NM Zinc, NM Amiloride-HCl, NM Hydrochlorothiazide, NM	Death
Grimmer et al. (2015) USA [5]	CR	1/29-year-old male	40 µg/twice daily	Oral	3 days	NM	Glutamine, NM Fibre supplements, NM Protein shakes, NM	Rhabdomyolysis, fever, tachycardia thirstiness, diaphoresis, shortness of breath
Santos et al. (2015) Portugal [32]	CR	1/25-year-old male	0.08 mg/day	NM	6 months	NM	Oxandrolone, 40 mg/day Mesterolone, 50 mg/day HGH, 10 IU/day Nandrolone, 600 mg/ biweekly Testosterone cypionate, 400 mg/biweekly Stanozolol, 100 mg/ triweekly Drostanolone, 200 mg/ triweekly Trenbolone 200 mg/ triweekly Testosterone propionate, 100 mg/triweekly Boldenone, 400 mg/ biweekly Methenolone, 200 mg/ biweekly	MI

Table 3 (continued)

Author (year) country (Ref)	Study design	Sample size/ patient(s) description	Dose/frequency of clenbuterol	ROA	Duration of use	Analytical findings	Concomitant therapies, dose	Adverse event
Mayer et al. (2016) Switzerland [83]	CR	1/22-year-old female	NM/NM	NM	NM	NM	Liothyronine, NM Levothyroxine, NM, Anastrozole, NM Dehydro-chlormethyl-testosterone, NM Stanozolol, NM IGF-1, NM Aldactone, NM Torsemide, NM Hormonal contraceptive pills, NM	Severe rhinovirus pneumonia
Matthew et al. (2017) USA [43]	CR	1/46-year-old male	NM/NM	Parenteral	NM	Blood: > 10 ng/ml	Boldenone undecylenate, NM Vitamin E, NM	Tachycardia, hypokalemia, hyperglycemia and hypotension
Mascagni et al. (2017) Italy [49]	CR	1/32-year-old male	NM/NM	NM	NM	NM	Hyperproteic diet, NM Ephedrine alkaloid, NM	Hepatic rupture
Zlak et al. (2017) Slovenia [84]	CR	1/34-year-old male	NM/NM	NM	NM	NM	Protein supplement, NM	Agitation, pain, hypotension, tachycardia, chest myocardial injury
Cheng et al. (2018) China [85]	CR	1/22-year-old male	80 µg/day	NM	10 days	NM	Stanozolol, 20 mg/day T_3, 25 µg/day	Cardiomyopathy, acute hepatic injury
Lehmann et al. (2019) Germany [41]	CR	1/34-year-old male	NM/NM	NM	NM	Blood: 1 µg/l or 1 ng/ml	Stanozolol, NM Metandienone, NM Trenbolone, NM Clomiphene NM	Death
Kintz et al. (2019) Turkey [40]	CR	1/61-year-old male	NM/NM	Oral	15 years	Blood:1.1 ng/ml Urine: 7.2 ng/ml bile: 2.4 ng/ml gastric content: 3.2 ng/ml, hair: 23 pg/mg	Stanozolol, NM	Death
Dufayet et al. (2020) France [52]	CR	1/17-year-old male	NM/NM	Oral	NM	Femoral blood: 9 ng/ml, Cardiac blood: 8 ng/ml, Urine: 25 ng/ml	2,4-dinitrophenol, NM Testosterone enanthate, NM Trenbolone enanthate, NM	Death

Table 3 (continued)

Author (year) country (Ref)	Study design	Sample size/ patient(s) description	Dose/frequency of clenbuterol	ROA	Duration of use	Analytical findings	Concomitant therapies, dose	Adverse event
Bonnar et al. (2021) Ireland [31]	CR	1/32-year-old male	NM/NM	Oral	NM	NM	T4, NM Growth Hormone, NM Trebolone, NM Stanozolol, NM Oxandrolone, NM Mesterolone, NM Fluoxymesterone, NM Drostanolone, NM	Hypokalemia, thyrotoxicosis factitial, hyperglycemia, metabolic alkalosis, myocardial injury, hypophosphatemia and hypomagnesemia

CR Case report, *NM* not mentioned, *CS* case series, *ROA* route of administration, *IU* international unit, *MI* myocardial infarction, *HGH* human growth hormone, *hCG* human chorionic gonadotropin

Effects on muscle

Grimmer et al. reported a case of rhabdomyolysis after taking clenbuterol in which a 29-year-old bodybuilder used 40 µg of clenbuterol twice daily for 3 days [5]. He had discolored urine and raised creatinine kinase level without acute kidney injury. Without experiencing any additional complications, the patient was successfully treated with standard therapy and released. The clear mechanism of clenbuterol-induced skeletal muscle damage is not completely understood. Chronic clenbuterol use has been linked to remodeling and functional impairment of fast-twitch skeletal muscle, according to experimental data from animals [28]. This medication may directly damage the sarcolemma, causing cytoskeletal and membrane protein damage. Similarly, stimulation of β2 adrenergic by clenbuterol led to the development of skeletal muscle necrosis in horses [29].

Effects on the cardiovascular function

Several incidences of cardiovascular adverse events after taking clenbuterol alone or in combination with other performing-enhancing drugs have been reported including arrhythmia, palpitation, chest pain, myocarditis, myocardial ischemia, and MI. A study from the poison information center by Spillar et al. also reported the occurrence of tachycardia, widened pulse pressure, ECG abnormalities, raised troponin and elevated creatine phosphokinase, palpitations, chest pain among bodybuilders, and fitness enthusiastic [7]. Two different studies from Poland and the USA reported the development of MI in young athletes who used clenbuterol monotherapy [25, 30]. Both the cases had no history of using an anabolic steroid, tobacco, and illicit drugs. It is noteworthy to mention that in the case from Poland the patient remains symptomatic despite serum clenbuterol concentration being undetectable [25]. Coronary vasospasm could be a possible mechanism of MI as both the patients had a normal coronary artery in coronary angiogram [25, 30, 31]. Similarly, another two incidences of MI were experienced by young bodybuilders concomitantly using anabolic steroids [31, 32]. Contributing role of clenbuterol in the development of infarction when administered with anabolic steroids is difficult to explore but synergistic effects possibly play role in the occurrence of MI in these cases [31]. The presence of a normal coronary artery further strongly suggests that coronary spasm was the cause of the infarct [31].

Another 2 cases of myocardial ischemia were reported by Huckins et al. in which both cases used clenbuterol alone [33]. Microvascular injury or endothelial dysfunction was the possible etiopathogenesis for the ischemia. In addition, the animal study reported the direct toxicity of clenbuterol on cardiac muscle cells [34]. It is well established that β2-receptor stimulation can have a direct effect

on coronary vessels, especially the smaller coronary arterioles [35]. Cardiac arrhythmia including supraventricular tachycardia, atrial fibrillation, and tachycardia were some other cardiovascular toxicities of clenbuterol reported in the study [8].

The clear mechanism of how clenbuterol causes arrhythmia is uncertain. Evidence from the published case studies suggests that selective β1-antagonist such as metoprolol counteract the toxic effects of clenbuterol on heart rate [8, 33]. This indicates that clenbuterol-induced arrhythmia could be due to the activation of β1 adrenergic receptors. Contrary to this, Gabriela et al. reported that clenbuterol induce stimulation of heart rate by acting on both $ß_1$ and $ß_2$ adrenergic receptors, and possibly an interaction of both the adrenoceptors play role in the attenuation of heart rate [36]. Electrolyte imbalance especially hypokalemia further increases the risk of cardiac arrhythmia. Spiller et al. reported a case of 25-year-old male who consumed 4.5 mg of clenbuterol which approximately 100 times more than the advised dose (20–40 µg BD) used for the treatment of asthma [7]. The reported toxicities included headache tachycardia, decrease blood potassium level, high blood sugar, ST changes on electrocardiography, raised troponin and creatine phosphokinase (CPK) level, palpitations, pain in chest, and tremor [7].

Effects on electrolytes balance

Electrolyte imbalance was reported by a 25-year-old man who consumed low dose (20 µg) clenbuterol monotherapy [10]. Immediately, he developed palpitation, chest pain, nausea, sweating, and anxiety. His biochemical investigation revealed hypokalemia, hypophosphatemia, hyperglycemia, and raised lactate and troponin [10]. This indicates that clenbuterol is capable of developing toxicity as low as 20 µg. Similar biochemical abnormalities were also reported from Ireland in which a bodybuilder concomitantly used anabolic steroid, and thyroxine [37]. Electrolyte disturbance was also reported by Hoffman et al. in which women consumed a fingertip quantity of clenbuterol [38]. The underlying mechanism of hypokalemia is most likely due to the activation of Na^+-K^+ ATPase in skeletal muscle mediated by beta 2 adrenoreceptors, resulting in an inward movement of potassium inside the cell [38]. Hypophosphatemia is attributed to the shift of phosphate ions from the extracellular compartment to the intracellular compartment as a consequence of hyperglycemia and hypomagnesemia is due to the intracellular sequestration of magnesium resulting from hyperglycemia [38]. Electrolyte disturbance may further potentiate the cardiotoxic potential of clenbuterol [39].

Effects on mortality

Kintz et al. reported the death of a 61-year-old bodybuilding trainer, clenbuterol 0.04 mg and stanozolol 10 mg was found in his room [40]. Post-mortem investigation revealed generalized organ congestion, and cardiomegaly [40]. Clenbuterol was found in all body tissues including blood, urine, bile, gastric content, and hair, whereas stanozolol was only found in hair. All other suspected drug abuse and alcohol were negative. The report concluded the cause of death is most likely due to cardiac insufficiency due to repetitive abuse of anabolic drugs [40]. Similarly, another incidence of death from cardiovascular complications was reported in a 34-year-old bodybuilder [41]. His cardiovascular examination revealed left ventricular hypertrophy and the right coronary artery showed a small vascular lumen. His blood investigation was positive for clenbuterol, stanozolol, trenbolone, and methandienone. Besides, his urine test showed the presence of boldenone, clomiphene, trenbolone, methandienone, stanozolol, clenbuterol, drostanolone, and testosterone. Clenbuterol in combination with other drugs is likely the cause of death due to cardiovascular failure [41]. Another incidence of death due to cardiovascular toxicities was reported to a 23-year-old man, who was taking clenbuterol along with anabolic steroids and other performance-enhancing drugs [42]. Cardiac hypertrophy, acute cellular necrosis, and interstitial fibrosis of the myocardium were reported to be the cause of his death [42]. The combination of anabolic steroids and clenbuterol can be the cause of myocardial infarction, even with a normal coronary artery in angiogram due to coronary spasm [31].

Other relevant consequences

Four different studies reported the incidence of hyperglycemia after taking clenbuterol for bodybuilding [9, 10, 33, 43]. Clenbuterol stimulates the secretion of glucocorticoids (cortisone and corticosterone) and inhibits the uptake of glucose in muscle and fat cells [44, 45]. A study has reported that clenbuterol reduced insulin sensitivity and decreased glycogen storage in hepatic cells [46]. Besides, it also affects the gene that is associated with glucose metabolism [46]. Hyperglycemia with clenbuterol is not uncommon. Clenbuterol-induced hypoglycemia was also reported in the pediatric population after accidental consumption of an unknown quantity of clenbuterol [47, 48]. Similarly, a study from the poison information center also reported clenbuterol-induced hyperglycemia and other metabolic abnormalities [16].

Two different case reports in our review documented the hepatic complication with clenbuterol [9, 49]. Though in both the reports, athletes concomitantly used other drugs but the role of clenbuterol in the development of liver toxicities could not be ruled out. An interventional study on human

reported that clenbuterol has a significant effect on weight loss but produce toxicity in the liver by forming lesions resulting in an increased level of liver enzymes [50]. Additionally, it also raised the triglyceride and LDL levels [50].

The effects of clenbuterol on kidney function are limited and unclear. Two different reports in our study documented acute renal toxicity and end-stage renal disease after taking clenbuterol [9, 51]. Clenbuterol was reported to accumulate in the kidney and its residues remain even after 28 days of withdrawal [35]. Consequently, it was considered that chronic use of clenbuterol increases the risk of kidney toxicities [35].

In summary, clenbuterol is prone to produce serious toxicities in almost all vital organs including the heart, liver, kidney, muscle, lungs, endocrine gland, and brain. Cardiac toxicity is the most common and life-threatening complication associated with this drug. Hepatic and renal dysfunctions, electrolyte imbalance, rhabdomyolysis, hyperglycemia, and death were the other major toxicities. Oral route was the most preferred route of administration among the abusers. Toxicity was seen to be developed as low as 20 µg, hence, difficult to predict the dose that may cause adverse effects. Toxicity was developed to acute as well as chronic abusers and polypharmacy was common among the clenbuterol users.

Clenbuterol and analytical finding

In this study, a total of 4 reports assessed the clenbuterol concentration in athletes [40, 41, 43, 52]. The clenbuterol level was reported as 1 ng/ml in two separate post-mortem examinations [40, 41]. The two deaths were traced back to cardiovascular complications. Clenbuterol and anabolic steroid usage were present in both instances. Therefore, despite the low levels of clenbuterol in the blood, it is likely that this combination was a significant contributor to the fatal outcome. Coronary spasm, even in the presence of normal coronary arteriograms, has been linked in the literature to myocardial infarction [25, 30]. Blood clenbuterol levels were reported to be 9 ng/ml in another post mortem report of athletes [52]. A high-ingested dose of clenbuterol may be the cause of these elevated values. In a study by Matthew et al., a body builder experienced tachycardia, hypokalemia, hyperglycemia, and hypotension, with a blood clenbuterol concentration of more than 10 ng/ml [43]. Plasma therapeutic concentration of clenbuterol lies from 0.3 to 0.6 ng/ml, and toxic concentration is 3 ng/ml in normal individual [53]. According to a study done by Girault et al., the average peak plasma level of clenbuterol in healthy adults after a single oral dose of 20 µg was 0.086 ng/ml [54]. Previous research among non-athletes documented a number of non-fatal incidents of clenbuterol toxicity. In a study, a 17-year-old girl who consumed 4000 µg of clenbuterol with the intention of decreasing weight was hospitalized 7 h later due to sinus tachycardia [55]. Her serum clenbuterol level was 5.9 ng/ml on day 1 and 2.6 ng/ml on day 2 [55]. Another study by Spillar et al., a 25-year-old man experienced cardiac toxicity after taking 4500 µg of clenbuterol, with a blood level of 2.98 ng/ml approximately 1 h later [7].

Before the 2019 revision of article 7.4 of the *World Anti-Doping Code*, there was no threshold for the detection of clenbuterol in doping test samples and even trace amounts resulted in AAFs and related penalties [56]. This revision introduced the option to report adverse atypical findings for this drug when detected at levels below 5 ng/ml of urine [57]. WADA has recognized hair testing is a viable alternative to doping control. Several studies reported the accumulation of clenbuterol in hair [58–60]. Despite low therapeutic dosages, clenbuterol can nevertheless be detected in hair after a single or occasional administration in horses. Hair clenbuterol residues as low as 0.02 pg/mg can be detected using a sensitive liquid chromatography tandem mass spectrometry (LC–MS/MS) technique [61]. Urine clenbuterol concentrations are transitory and subject to individual influences such as renal excretion, hair concentrations represent a more stable mean value over the course of weeks or months. Clenbuterol, being a lipophilic molecule, binds to hair pigment strongly and irreversibly [58, 62]. Hence, hair clenbuterol concentration will be useful for carrying out follow-up studies of suspected doping cases. A sub-therapeutic dose of clenbuterol was administered to twenty healthy volunteers on 5 consecutive days. One month after the administration began clenbuterol was found in the proximal hair Section (0–1 cm) at values ranging from 0.43 to 4.76 pg/mg [61]. The occurrence of adverse analytical findings (AAFs) for clenbuterol by WADA-accredited laboratories in last ten years is presented in Fig. 2 [63–72].

Regulatory status and challenges of clenbuterol abused

Clenbuterol is not a controlled substance under the controlled substance act however, owing to its performance-enhancement effects it is banned by World Anti-Doping Agency and the International Olympic Committee [11]. The regulatory statuses of clenbuterol in different countries are presented in Table 4.

Clenbuterol showed a significant increase in skeletal muscle and a reduction in body fat deposition in an animal study [73]. However, similar effects of clenbuterol were never proved through human study. Neither its safe dose range has been established through a clinical trial. Indeed, athletes use this drug illegally because they think it will increase their athletic performance. Health care professionals consider the use of clenbuterol among athletes

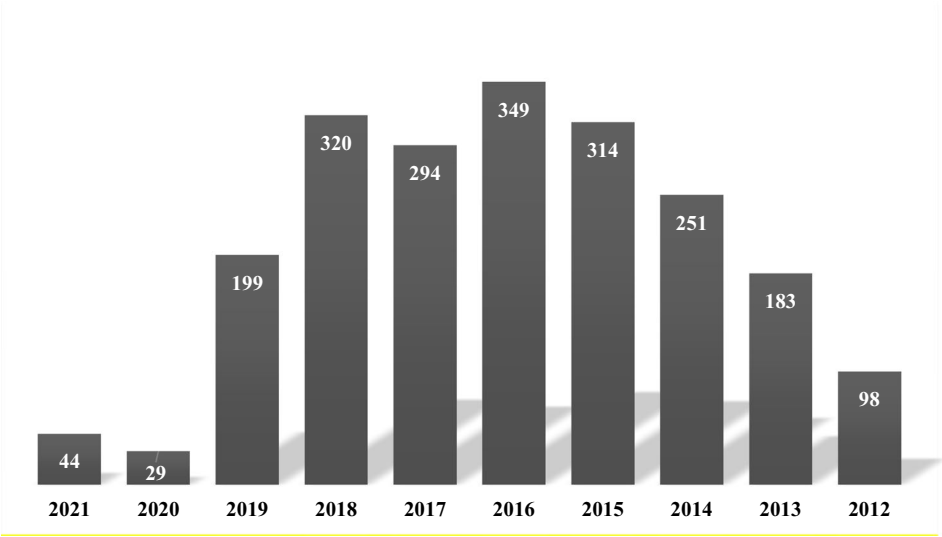

Fig. 2 Number of adverse analytical findings for clenbuterol in the past ten years in laboratories accredited by the World Anti-Doping Agency (WADA)

Table 4 Regulatory status of clenbuterol in different countries

Country	Regulatory status	Reference
Italy	It is used for the treatment of asthma and COPD	[23]
Germany	Clenbuterol is approved for humans in the treatment of asthma. For adults and children over the age of 12, a total daily dose of 40 µg/day is recommended	[8, 24]
US	For human use, clenbuterol is not approved. It is used (0.8–3.2 µg/kg twice daily) to treat respiratory issues in horses	[26]
India	Clenbuterol alone or as an adjuvant is approved for respiratory diseases of horses	[87]
Australia	It is a prescription-only drug approved for particular medical conditions. These medications are not permitted for use in performance or appearance enhancement, though. Approved for use in veterinary medicine under schedule 4	[74]
UK	It is prohibited to purchase this drug because it is a controlled substance of class C	[88]
Canada	This drug is approved for veterinary use only. Administration of this drug in animals that are used as food by humans is prohibited	[89]
China	Manufacturing, sales, and the use of clenbuterol are banned	[90]

unjustified as the risk outweighs the benefits. Clenbuterol is a prescription-only drug in many countries [24, 74]. Despite it being easily available in the market, several professional sports athletes from different countries tested positive for clenbuterol and were disqualified from sports [75]. Athletes obtained this drug from the health supplement market or import it from other countries where it is licensed for human use [76]. Interestingly, it is advertised on the internet as a fat burner, treatment for obesity, cutting and lean muscle supplement, and weight loss agent. This misleading information and online marketing led to its widespread use. Spillar et al. reported several cases of clenbuterol abuse after consuming weight loss supplements [7]. Indicating the widespread and easy availability of this drug, it was also found to be adulterated with street drugs such as heroin and cocaine [77]. In addition, extensive clenbuterol misuse as a growth-promoting agent in lamb, bovine, and pigs was well documented in many parts of the globe including China, Mexico [78], and Portugal [26]. This is how humans can unwillingly become positive upon consumption of clenbuterol-contaminated meat. Despite the ban on the illegal use of clenbuterol in animal production and abuse/doping by athletes, this drug is easily misused. Due to the growing number of clenbuterol misuse and associated complications policies need to be formulated to prevent the illegal marketing and import of this drug. Future efforts should also be focused on preventive strategy by creating awareness among athletes, sports physicians, fitness coaches, teachers, and parents.

Role of pharmacist in prevention and control of clenbuterol abuse

Problems involving the use of clenbuterol among professional athletes and exercise fanatics are underreported. There is a lack of reliable data regarding the usage pattern of this drug including drug-drug interaction, dose, adverse reaction, and serious adverse reaction. Many athletes procure this drug from coaches, friends, physicians, or other health care workers and even directly purchase it by themselves online. Polypharmacy is common among athletes which

increase the risk of drug–drug interaction and adverse outcomes [79]. Pharmacists possess adequate knowledge of the drugs including those that are subject to abuse by athletes. Pharmacists may help in the selection of non-prescription drugs and health care supplements for professional athletes and exercise enthusiasts and can assist the athletes in avoiding the banned products. They may oppose the sale of clenbuterol or clenbuterol-containing products in pharmacies. They can deliver talks to school, colleges, fitness center, and the community about drug abuse and prevention programs, and creates awareness of the adverse health consequences of illegal drugs and the penalties associated with them. They may also provide evidence-based updated information to drug abuse counselors regarding the pharmacology of clenbuterol and its adverse health consequences and detoxification. Pharmacists can work with the drug regulatory authority to control the illegal use of the drug. Pharmacists should have the relevant knowledge to advise patients on strategies for avoiding to use clenbuterol, and may direct athletes to seek safe and alternative options including nutrition, training strategy, and development of psychological skills [80]. Government should also take appropriate measures to curb the illegal supply of clenbuterol including supply via the internet.

Conclusions

Several cases of adverse events have been reported, and most of them have serious consequences including death. The use of clenbuterol among athletes is increasing; hence, clenbuterol exposure should be taken into consideration in patients admitted with sympathomimetic effects after consuming health supplements. There is an urgent need of creating awareness among teachers, parents, students, young athletes, gym-goers, and trainers, regarding the potential danger associated with clenbuterol abuse. Additionally, the easy availability and unregulated use of performance-enhancing drugs in the era of online marketing contributed to the tragic incidences of adverse health outcomes. Therefore, appropriate regulatory measure has to be taken to prevent the illegal marketing of this drug.

Data availability All the required data are available with manuscript.

Declarations

Competing interests The authors declare no competing interests.

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