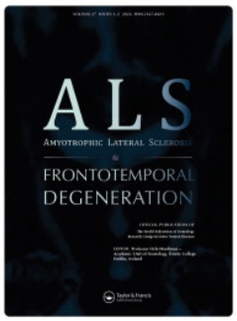

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ALS untangled #83: clenbuterol

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RESEARCH ARTICLE

ALS untangled #83: clenbuterol

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Abstract

ALS Untangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here we review clenbuterol, a β-2 adrenergic agonist, as a potential treatment for amyotrophic lateral sclerosis (ALS). Clenbuterol has biological effects that could be relevant to the pathophysiology of ALS such as inducing muscle hypertrophy, improving mitochondrial function, and reducing neuroinflammation. Two studies in mouse models of motor neuron disease and two open label trials suggest possible benefits. However these have methodological flaws which limit interpretation. Clenbuterol can have an array of side effects, some severe. Drop-outs due to side effects were very common in one of the ALS trials and in a separate expanded access program. Based on this information, we cannot currently

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endorse clenbuterol as an ALS treatment, but we do hope to see further studies of it, or another long acting β-2 adrenergic agonist in people with ALS.

Keywords: *ALS; clenbuterol; β-2 adrenergic agonist; muscle atrophy; neurodegeneration*

Overview

Clenbuterol is an oral medication that is a selective agonist of β-2 adrenergic receptors (β2AR, 1–3). β2AR are G-protein coupled receptors present in cellular membranes of various tissues including smooth muscle such as bronchioles and blood vessels, skeletal muscle, neurons and glia within the central nervous system (1). Studies in human volunteers have shown clenbuterol to possess a long half-life of approximately 35 hours and is primarily eliminated by renal excretion (4,5).

Originally patented in 1967, clenbuterol became available in several countries in the late 1970s for management of respiratory conditions including asthma and chronic obstructive pulmonary disease (COPD) due to its effects as a long-acting bronchodilator (6). The drug is typically formulated as clenbuterol hydrochloride salt and can be administered as an oral tablet or liquid. The medication never entered widespread medical practice and was never approved by the US Food and Drug Administration (FDA) due to concerns about systemic side effects, especially cardiac effects such as tachycardia and arrhythmias (7). Nonetheless, clenbuterol entered use in parts of Latin America and Europe during the 1980s and remains available in limited countries in Latin America, eastern Europe, and Asia (8,9). Despite never receiving approval for human use in many countries, clenbuterol did receive approval in veterinary medicine for pulmonary disease in horses in the USA (7).

Clenbuterol also gained a reputation for potential benefits to muscle hypertrophy and fat loss (10). Due to concerns for potential abuse, clenbuterol and other β-2 agonists were banned from use by athletes in 1972 by the International Olympic Committee (11). Nonetheless, an underground market emerged for sale of clenbuterol among bodybuilders and influencers promoting it for weight loss where it became known as "clen" or less commonly "bute." The World Anti-Doping Agency (WADA) has included clenbuterol in all updates of its prohibited list since it was first adopted in 2004 (12). Clenbuterol was also used in the livestock industry to promote leaner meat for consumption until it was banned from use in food-producing livestock in the US in 1991 due to concerns about adverse effects in consumers (13).

This review will discuss the potential role of clenbuterol in ALS treatment.

Mechanisms of action

The primary mechanism of action of clenbuterol is β-2 agonism which has been shown to induce downstream effects that could be beneficial in the treatment of ALS (14,15, Figure 1). β-adrenergic receptors are cell membrane-spanning receptors that are present in many different types of tissue (1). β2AR is a G-protein coupled receptor (GPCR), and activation of β2AR by agonists such as clenbuterol leads to intracellular activation of the enzyme adenylyl cyclase followed by production of the second messenger cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA) (1,2). PKA is then able to activate other proteins through phosphorylation including the cAMP-response element binding protein (CREB) which functions as a transcription factor for numerous genes (1,15).

β adrenergic receptors are present in regions of the human central nervous system involved in the pathology of ALS including in the motor cortex and spinal cord, though studies seem to suggest a higher proportion of β1AR compared to β2AR (16). A study in rats specifically demonstrated the presence of adrenergic receptors on cortical pyramidal neurons as well on α-motor neurons within the gray matter of the spinal cord (17).

Effects on neuronal growth factors

Within neurons, activation of β2AR and the resulting cAMP/PKA/CREB pathway triggers increased expression of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) which support the growth and maintenance of neurons (1,18).

Effects on glutamate-mediated neuronal toxicity

β-2 agonists may also protect against pathological protease activity caused by glutamate toxicity, a key factor in neuronal death in ALS (1,19). Prolonged excitation of neurons with glutamate results in excessive intracellular calcium and stimulation of calcium-dependent proteases called calpains. Although not yet demonstrated within neurons, β2AR activation in skeletal muscle appears to inhibit calpain activity through increased expression of the inhibitory protein calpastatin (20,21).

Effects on neuroinflammation

β2AR have been found on glial cells including microglia and astrocytes which are present throughout the nervous system (22,23). Within astrocytes, β-2 agonism appears to decrease activity of a pro-inflammatory pathway involving nuclear factor kappa-light-chain-enhancer of activated B cells

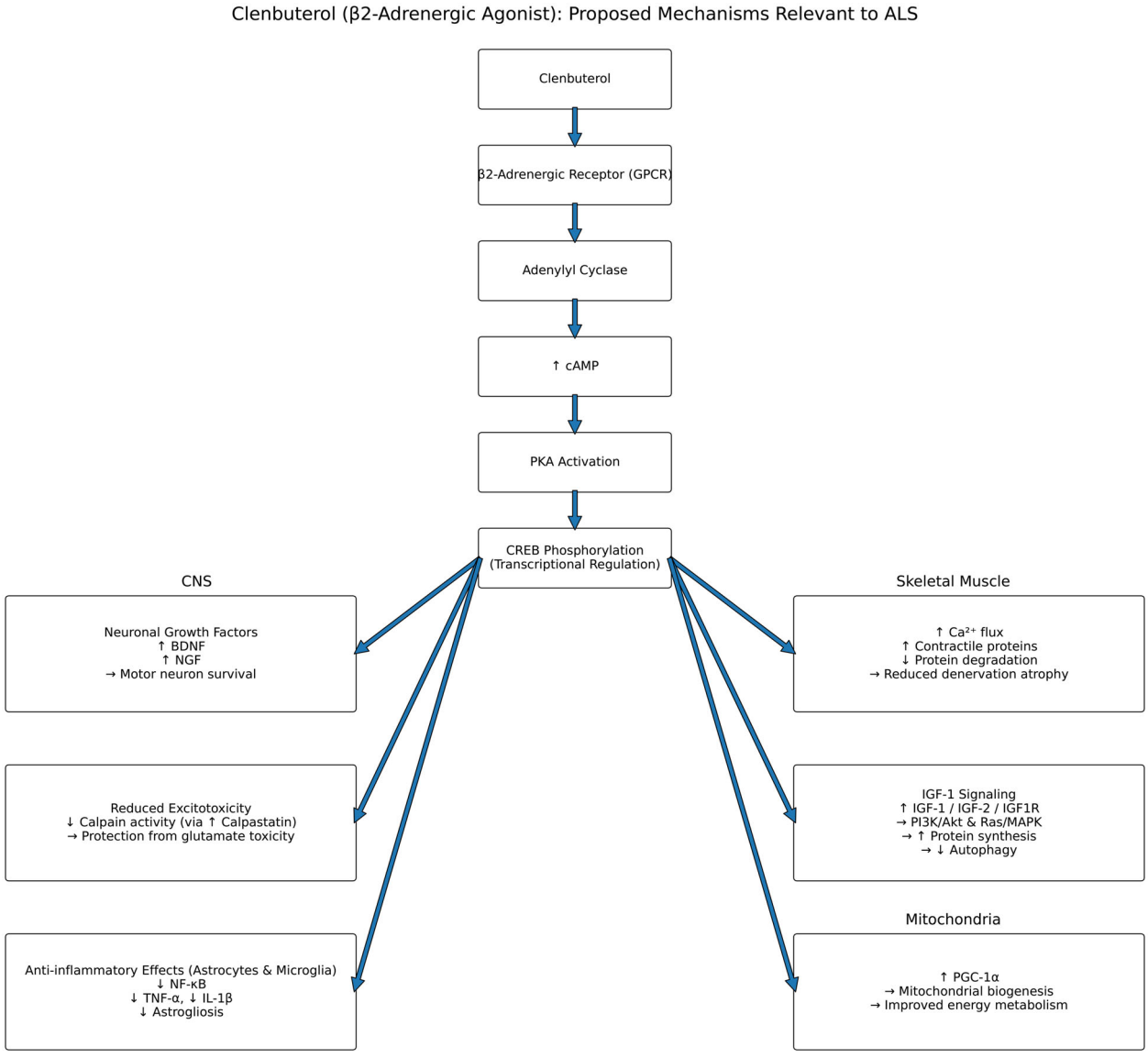

Figure 1. This figure shows clenbuterol's ALSrelevant mechanisms of action.

(NF-κB) thereby decreasing expression of inflammatory cytokines tumor necrosis factor α (TNF- α) and interleukin 1β (IL-1β). Furthermore, there is evidence that β-2 agonism can inhibit the proliferation of both microglia and astrocytes within the CNS, thereby reducing astrogliosis and inflammation and promoting neuronal recovery after injuries (22–24).

Effects on muscle function in setting of denervation

β-adrenergic receptors are also highly expressed in skeletal muscle with up to 90% being the β2AR subtype (25). The effects of β-2 stimulation on skeletal muscle fibers include increased calcium flux into and out of the sarcoplasmic reticulum contributing to increased muscle contractile strength, increased expression of contractile proteins, and inhibition of protein degradation (26). Clenbuterol administration has also been demonstrated to reduce muscle atrophy in cases of denervation in a randomized controlled trial (27).

Influence on insulin-like growth factor signaling and autophagy

Multiple studies in animal models and in PALS have shown that increased IGF-1 levels are associated with better prognosis and improved survival in ALS (28,29). Although trials administering subcutaneous IGF-1 to patients with ALS had largely disappointing results, the employed dosing strategy in most of these trials may have been inadequate (reviewed in 30). IGF-1 signaling is known to stimulate skeletal muscle stem cells, also known as satellite cells, to propagate and differentiate into myoblasts to contribute to formation of new muscle fibers (31). Expression of IGF-1 increased not only within muscle cells, but also within neurons, and this signaling plays a major role in promotion of neurogenesis and synaptogenesis (32). As previously discussed, activation of the cAMP/PKA pathway by β2AR activates the transcription factor CREB to affect the expression of various genes involved in muscle

Table 1. Table of evidence for clenbuterol.

	Grade	Explanation
Mechanism	A	Shown in peer-reviewed publications to act on relevant mechanisms of neuroprotection, muscle hypertrophy, and mitochondrial function
Pre-Clinical	C	Flawed study in G93A mSOD1 mice suggested that clenbuterol delayed disease onset and slowed progression
Cases	D	Single subjective report of benefit in a PatientsLikeMe participant, without independent confirmation of benefit
Trials	D	Two small trials suggested possible benefits for PALS, but these trials were very small, and were not randomized, blinded or placebo controlled.
Risks	D	Side effects are common as the dose of clenbuterol increases. Medication toxicity can result in serious adverse cardiac events, electrolyte disturbances, or potentially death.

metabolism. One such effect is the increased expression of insulin-like growth factor (IGF)-1, IGF-2, and their corresponding receptors IGF1R and IGF2R (33,34). IGF-1 signaling is known to be highly associated with skeletal muscle anabolism via activation of the PI3K/Akt and Ras/MAPK signaling pathways which lead to increased protein synthesis, inhibition of protein degradation by the ubiquitin-proteasome system, and reduced autophagy (31).

Mitochondrial effects

β2AR signaling supports the function and biogenesis of mitochondria, organelles responsible for the majority of cellular energy production and whose dysfunction is a known feature of ALS (22,35,36). The beneficial effects of β-2 agonism appear to be primarily mediated by increased expression and/or direct activation of peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) which is a crucial regulator protein in mitochondrial biogenesis (37).

As clenbuterol has been shown to positively influence several mechanisms relevant to ALS (Figure 1), including in humans, ALSUntangled assigns a TOE 'Mechanism' grade of A (Table 1).

Pre-clinical models

Two studies of clenbuterol in animal models of motor neuron disease show promising results. A 2004 study by Zeman et al. studied the effects of clenbuterol in a mouse model of neuronal ceroid lipofuscinosis (NCL), a lysosomal storage disease which leads to progressive neurodegeneration, most predominant within motor neurons (38). When compared to mice that did not receive clenbuterol, those treated with approximately 1 mg/kg of clenbuterol daily showed significantly delayed onset and progression of motor dysfunction as evidenced by improved grip strength and behavioral tests at 9 months of age. Clenbuterol increased grip strength in NCL-model mice by 61% as compared to untreated mice and demonstrated an increase in mass of tested muscles by up to 41%. Additionally, the motor neurons in clenbuterol-treated mice saw a 39% reduction in eccentrically displaced nuclei, a known marker of neurodegeneration (39). Some of our team members felt that this model was less relevant to ALS than the G93A-mutant SOD1 model.

A second study published in 2006 tested clenbuterol in this G93A-mutant SOD1 mouse model of ALS (40). Mice received either 1.5 mg/kg daily of intraperitoneal clenbuterol or an equivalent volume of saline. G93A-SOD1 mutant mice treated with clenbuterol showed statistically significant delayed disease progression and motor dysfunction as well as increased longevity compared to those that did not receive clenbuterol (40). Critiques of this study include its very small sample size ($n = 18$), lack of randomization or blinding.

Given these pre-clinical studies of clenbuterol in mouse models of motor neuron disease, one of which is widely recognized as a model of ALS (G93A-mutant SOD1) we assign a TOE score of C for 'Pre-clinical Models' (Table 1).

Cases

In the online community PatientsLikeMe, five members report trialing clenbuterol with only two evaluations available for review which were split in terms of perceived effectiveness. No more details on effectiveness were available. Common reported side effects included clonus/spasms as well as irritability and were rated as moderate (41).

In the ALS Therapy Development Institute's ALS Research Collaborative Database (ALS-TDI ARC, 42), we found 3 participants who reported starting clenbuterol during the collection of their self-reported ALSFRS-R scores. ALSFRS-R slope before and after starting clenbuterol appeared similar. Limitations to this data are the fact that ALSFRS-R scores are self-reported, and that we do not know of some of these individuals may have stopped the treatment at some point in their follow up.

Based upon the single PatientsLikeMe participant reporting subjective improvement, we assign a TOE 'Cases' grade of D (Table 1)

Trials/expanded access programs

To date, there are two small trials of clenbuterol in PALS. A pilot trial of clenbuterol conducted in Italy (43). This study included 16 participants with ALS by the El Escorial criteria (44). All patients were receiving riluzole 50 mg twice daily. Disease duration was not specified. Baseline ALSFRS-R score was 22. Patients were treated with clenbuterol 20 μg three times a day (for comparison to the animal studies, this is approximately 0.001 mg/kg). Participants tolerated the medication well with few reported side effects (hand tremors, fasciculations, cramps, and nervousness) of which all resolved with continued clenbuterol use. No adverse cardiac effects, changes in heart rate, or electrolyte abnormalities were observed. Fourteen patients completed the study; No patient dropped out due to side effects. A statistically significant improvement in strength (as measured by myometry) occurred between baseline at the three-month evaluation (20% in upper extremities and 22% in lower extremities) with sustained improvement at the six-month evaluation (23% in upper extremities and 27% in lower extremities). Twelve of the participants completed spirometry assessments which revealed a 10% improvement in mean forced vital capacity (FVC) after six months. No statistically significant change was seen in another measure of muscle strength (mean composite Medical Research Council score) or ALS Functional Rating scale during the study.

A more recent open-label trial of clenbuterol in PALS was conducted at Duke ALS Clinic (14). The included 25 participants with ALS by the El Escorial criteria (44). Seventeen participants were also taking riluzole, but they were required to be on a stable dose for at least 30 days prior to study enrollment. Mean disease duration was 43 months, baseline ALSFRS-R score was 34. Participants started with an initial titration over 7 weeks up to 80 μg twice daily of clenbuterol which was then continued for the remaining duration of the 24-week trial. Of the 25 participants, 13 withdrew from the trial due to side effects. The most common side effects seen were tremors, cramps, and insomnia. No severe adverse events related to clenbuterol were observed. Intention to treat analysis of 16 participants who took at least one dose of clenbuterol and had at least one FVC measurement post-treatment showed a statistically significant slowing of FVC decline during clenbuterol treatment compared to before treatment, $p = 0.02$. Intention to treat analysis of 20 participants who took at least one dose of clenbuterol and had at least one ALSFRS-R measurement post-treatment showed a trend toward slower progression on clenbuterol (−0.33 points per month) compared to before treatment (−0.52 points per month) though this finding did not reach statistical significance (14). This trial was appropriately criticized in a letter to the editor, which pointed out its lack of randomization or blinding, small sample size, large dropout rate, and lack of placebo control (45). Another potential problem arises when comparing ALSFRS-R or FVC progression before and after treatment; this comparison assumes that the natural history of progression on these measures is linear, which is disputable (46).

At the Healey & AMG Center for ALS at Mass General Hospital, Clenbuterol was provided to 11 PALS through an FDA-regulated intermediate size expanded access program (IND number: 170597). Eligible participants were diagnosed with either possible, probable, laboratory-supported probable, or definite ALS as defined by the El Escorial Revised ALS diagnostic criteria. All participants were also not eligible for any ongoing clinical trials.

Based on previous clinical trial experience with Clenbuterol, the dose was titrated in a stepwise manner to minimize potential adverse events (14). Participants started at 20 micrograms twice daily for four weeks. If tolerated, they could increase to 60 micrograms daily for two weeks, then to 90 micrograms daily for the remainder of the program. Clenbuterol was sourced through everyone.org (The Socialized MedWork) in 100 tablet blister packets, each containing 20 micrograms of Clenbuterol.

Visits were scheduled at four-, eight-, or twelve-week intervals for up to 84 weeks. Safety monitoring was done through adverse event and concomitant medication review, electrocardiograms (ECGs), ALSFRS-R questionnaire, and safety labs. Due to the progressed patient population, visits could be done via telemedicine to minimize patient travel burden. If participants could attend in-person visits, slow vital capacity (SVC) breathing tests were also performed.

Eleven participants received Clenbuterol for up to 72 weeks (average: 12 weeks; range: 0–72 weeks). The average ALSFRS-R score at Screening was 20.3. The most commonly reported adverse events deemed related and expected to Clenbuterol were tachycardia, hypertension, anxiety, nausea, fasciculations, jitteriness, and cramping. One participant had an elevated Creatine Kinase (CK) value that was deemed expected and related to Clenbuterol. No other clinically significant changes in laboratory values or ECGs were observed. Four participants discontinued treatment with Clenbuterol because of side effects. Three participants discontinued to pursue different treatments that were contraindicated with Clenbuterol. Three participants discontinued

due to respiratory failure deemed related to ALS disease progression. Six participants reached the highest dose. Since this expanded access program was designed for compassionate use, no efficacy analyses were conducted.

While both the above trials showed benefits, these (and the expanded access program) were all small, and were not randomized, blinded or placebo controlled. Therefore, we assign a 'Trials' TOE grade of D (Table 1).

Dosing, risks, costs

The optimal dose or formulation of clenbuterol for treating ALS (if any) is not known. Clenbuterol has never been approved by the FDA for use in the humans in the US and its use is limited in medical practice around the world (7–9). It is typically formulated as clenbuterol hydrochloride salt which can be administered as a tablet or liquid solution (7). Online pharmacies servicing other countries currently list clenbuterol in 20, 40, or 60 μg tablet formulations available from approximately 1.5 to 3 USD per tablet (47).

As far as safety and tolerability, reports vary widely and are at least somewhat dependent on the underlying condition and the dosage used. For example, in a small study of patients with reversible airway restriction (9), a dose of 60 μg daily was safe and associated with only minor side effects including Cough (21%), headache (10%), nausea (7%) and dizziness (3%). This same dose was similarly well tolerated in one of the open-label ALS trials (43). In contrast, in the open label ALS trial at Duke, higher doses (80 μg twice daily) were not as well tolerated and tremors, cramps, and insomnia led to significant drop out. The MGH expanded access program also had a very high dropout rate due to side effects. Use of clenbuterol for weight loss and performance enhancement, typically (though not always) at much higher doses than those used in reversible airway disease, has been associated with agitation, palpitations, tachycardia, atrial fibrillation, hypokalemia, and hyperglycemia (48,49). In extreme cases, myocarditis, type II myocardial infarction, and/or death have been reported (50,51). In body builders, doses as low as 20ug daily have rarely been reported to cause cardiac side effects (48,52). Clenbuterol toxicity is typically treated with supportive measures to include IV fluids, electrolyte repletion, and β-blockers (49).

It should be noted that the elimination half-life (25–39 hours) of clenbuterol may be prolonged in patients with impaired renal or hepatic function (4,5). Clenbuterol should not be combined with other adrenergic agonist medications and should be used with caution with anti-cholinergics, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants to avoid increased risk of arrythmia (1).

While the majority of clenbuterol's side effects across conditions appear to be mild to moderate, especially at lower doses, based on the rare reports of serious adverse events including myocardial infarction and death, we assign clenbuterol a TOE "Risks" grade of D (Table 1).

Conclusion

Clenbuterol's effects on neuroinflammation, muscle hypertrophy, and mitochondrial activity appear potentially relevant to ALS disease pathology. Data in murine models of motor neuron disease as well as two small flawed clinical trials in PALS are also somewhat promising but due to the small sample sizes, lack of randomization or blinding or placebo controls, these must be viewed with caution. In these trials, lower doses (60 μg daily) were better tolerated than higher doses (80 μg twice daily). Clenbuterol has potentially serious adverse cardiac effects at higher doses, and it is not currently approved by the FDA for use in humans in the US. Most of us believe clenbuterol deserves further investigation in ALS, but it cannot currently be endorsed as an effective or safe ALS treatment. There are other beta agonists that may be safer and more feasible easier to study (1); we are aware of one (salbutamol) is going into the Experts ALS Trial (53) in 2026 (personal communication between RB and CM) and another (CuraCM) (54) that is being developed for multiple indications.

Declaration of interest

Dr. Bedlack is a paid consultant for Curasen, whose product is mentioned in this paper.

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Data availability statement

There is no dataset associated with this manuscript.

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