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Letter to the Editor

Whether or Not Clenbuterol is Beneficial in Sporadic ALS can only be Answered through Appropriately Designed Studies

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We read with interest the article by Li *et al*. about an open-label cohort study of 25 patients with sporadic amyotrophic lateral sclerosis on the effects of clenbuterol (80 microgram twice daily) over an observational period of 24 weeks [1]. ALSFRS-R and FVC progression were to slow according to per-protocol and intention-to-treat analyses [1]. Changes in hand grip dynamometry and myometry varied widely, most regressed slowly but some showed improvements [1]. It was concluded that clenbuterol slows ALS disease progression [1]. The study is impressive, but some points require discussion.

The major limitation of the study is the design an open-label design has the disadvantage that there is the possibility for missing data due to knowledge of the assigned treatment and the expectations of those involved in the trial [2]. If the amount of missing data is large, it is not clear whether the overall trial result would have been different if the data had not been missing [2]. The open-label design also has the disadvantage that there is no randomisation, no blinding, and no placebo controls. In order to assess the effect of medications, it is important to conduct a completely blinded study.

A second limitation of the study is that the number of included patients was small and the number of drop outs was high (n=13). A study with a small number of patients (n=11) has the disadvantage, that the patient sample may not be representative of the entire patient group and that therefore the findings may not be applicable to the entire patient group. Overcoming this drawback would have required the conduct of a well-powered, multicentre, multinational study.

A third limitation is that the studied cohort was very heterogeneous in terms of disease stage, ALS type, riluzole use, and co-medications. If the effect of clenbuterol depends on the disease stage, only patients with the same or similar disease stage would need to be included. Clenbuterol can have different effects on limb and bulbar onset ALS. Therefore, we should know how many had bulbar and how many limb onset ALS. Assuming that clenbuterol interacts with riluzole, it can be speculated that those who took riluzole had a different effect from clenbuterol than those who did not take it. Although it was not specified which medications the enrolled patients were regularly taking in addition to the study drug or riluzole, it can be assumed that at least some of the patients have taken co-medications that could have influenced the effects of clenbuterol. Therefore, it must be requested, that the co-medications be provided from all included patients.

A fourth limitation is that the patients were diagnosed using the El Escorial criteria, which are the oldest for diagnosing ALS. The most current criteria for diagnosing ALS are the Cold coast criteria, so it should be assessed whether the included patients also met the Gold coast criteria [3] and how many of the patients who had ALS according to the El Escorial criteria did not meet the Gold coast criteria.

There is a discrepancy between the statement “no conclusion could be drawn regarding the effectiveness of clenbuterol” and the statement in the conclusion that “the study shows that clenbuteraol slows ALS disease progression” [1]. This discrepancy should be resolved.

Overall, the interesting study has shortcomings that raise doubts about the conclusions and their interpretation. Clarifying these deficiencies could improve the results and conclusion of the study. Whether clenbuterol actually has a beneficial effect on ALS patients needs to be examined in a blinded, randomised, placebo-controlled trial. Assessment of the effect of clenbuterol on ALS patients may be biased if only an open-label, uncontrolled design is chosen and if the study population is small.

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