Letter to editors

Dear Editors,

On behalf of the Project Ethics Council of TREAT-NMD (http://www.treat-nmd.eu/), an international network linking together advocacy groups and researchers with an interest in the neuromuscular field, we would like to bring the following to your attention: there is currently much research ongoing towards developing treatments for neuromuscular disorders, of which the results are published in journals like yours. Individuals affected by these severe and progressive diseases are eagerly waiting for treatments for themselves, or in case of childhood diseases, treatments for their child. Indeed every day counts for these conditions, because when a critical function is lost (e.g. ambulation, self feeding etc) this might not be ever regained. As such these patients and parents are vulnerable to scientists overselling their results in scientific publication. This can be through exaggeration of findings in clinical trials in the abstract or the text, but also overselling the implications of results in pre-clinical models. While results in cell or animal models may well be encouraging, many additional steps are required before a new approach can be taken into the clinic to test if it is effective and safe in patients. Failing to outline the stage of the research (early or late in the drug development trajectory) and exaggerating results often leads to therapeutic misconception with patients or parents. While scientific publications are aimed primarily at researchers and not at patients and parents, in this day and age, the patient community does have access to these publications. Organisations like ours deal on a daily basis with patients who have been affected by therapeutic misconception due to inconsistent claims in scientific manuscripts.

Too often authors of scientific manuscripts do not pay attention to the many factors which may influence the possibilities of translating results in cell lines and animal models to patients. In Duchenne muscular dystrophy (a common and very severely progressive childhood neuromuscular disorder) there are indexed in pubmed for example more than 1000 publications claiming therapeutic success in animal or cellular models. In reality, only a handful led to clinical trials and so far only one product is conditionally approved and then, only in Europe. These facts emphasize why authors should use caution when reporting on potential therapies in development.

Notably, for products that are already on the market for other indications, overselling or hyping results is even more dangerous. This may lead to the off-label use of drugs based on studies in animal models, which may have adverse or even dangerous effects when used in patients. We would like to illustrate this with two recent examples: High doses of sildenafil (Viagra) protected the *mdx* mouse model (a model for Duchenne muscular dystrophy) from skeletal muscle damage and improved heart function (see http://www.ncbi.nlm.nih.gov/pubmed/18474859 and http://www.ncbi.nlm.nih.gov/pubmed/20956307 and http://www.ncbi.nlm.nih.gov/pubmed/22653783). Based on these publications we have been contacted by many families who bought Viagra online to treat their children. In parallel, a placebo controlled trial was set up to assess the effect of Viagra in Duchenne patients.

Unfortunately, this trial revealed that Viagra did nothing whatsoever to prevent muscle damage and was, if anything, detrimental for heart function to the point that the Data Safety Committee prematurely terminated the study (http://www.ncbi.nlm.nih.gov/pubmed/25042693). Another phosphodiesterase 5 inhibitor, Tadalafil, which has better pharmacokinetic properties than Viagra, is currently being evaluated in a large phase 3 clinical trial (http://www.clinicaltrials.gov/ct2/show/NCT01865084?term=NCT01865084&rank=1).

Regarding clinical studies, a recent publication suggested that certain supplements (vitamins and the like) slowed down disease progression in facioscapulohumoral muscular dystrophy. The results on benefit are portrayed as very positive, while only a marginal effect can be observed in the data provided. Patients who read these very encouraging data- based in a handful of patients in a single centre- are now seeking to obtain these supplements which can be bought without prescription. However, when these supplements are used at higher quantities than the recommended dose, they can lead to side effects - a risk that is not addressed in the paper. When patients have raised expectations from compounds, based on how the results in the paper are portrayed, there is a real concern that overdosing could occur when the anticipated beneficial effect fails to materialize.

We would ask you to urge your reviewers to have particular consideration for the potential risks that arise when an author overstates the potential benefits of their work. Positive results may of course be reported, but they should be backed up by data and words such as ‘cure’ should be reserved only for treatments that really cure the disease and not for treatments that will slow down disease progression. We feel that the rigor with which any claim related to therapeutic benefit is assessed during the editorial review in your journal should be the same as other content of any other section of the manuscript, so that the value of these manuscripts will be improved, and the risk of therapeutic misconception, which severely affects the very patient population which is the object of these studies, can be avoided in the future

We thank you in advance for your consideration.

Yours sincerely,

On behalf of the TREAT-NMD Project Ethics Council

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