The challenges of estimating multi-state model transitions in rare diseases: Informing an economic decision model for Duchenne Muscular Dystrophy

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Introduction

Duchenne Muscular Dystrophy (DMD) is a rare disease resulting in limited information (from disparate sources) on the natural history of the disease. This work synthesised data from the literature in order to perform a unified analysis to estimate transitions in a multi-state natural history model, and which could be used to inform future economic decision models.

Methods

Identifying data sources: A literature review was performed to identify Kaplan-Meier (KM) curves to inform transitions in the early/late ambulatory/non-ambulatory progression multi-state model.

Synthesising data: KM curves were digitized to obtain estimated individual patient data (IPD). Transitions with limited available data were supplemented with parametric models, based on the assumptions in Landfeldt et al [1].

Data analysis: Flexible parametric survival models were fit to transitions informed by digitized data. Available covariates were included for the relevant transitions and informed transitions were stratified by data source. Age was used as the timescale. Transition probabilities and length of stay were obtained for different covariate values, standardised over the data sources.

Software: KM curves were digitized using WebPlotDigitizer [2] and converted into estimated IPD using the Stata command *ipdfc* [3]. Multi-state post estimation was performed using the Stata command *predictms*, part of the multistate package [4].

Results

Identifying data sources: 3 KM curves reporting loss of ambulation were found (and were of sufficient quality to digitize with steroid use known). The early and late ambulatory stages were therefore collapsed (Fig. 1). No sufficient quality KM curves, with the appropriate time scale, for the other transitions were found.

Synthesising data:

- Ambulatory > Early non-ambulatory: There tails in the KM curves were poorly replicated with the digitized data (due to incomplete reporting of analyses). This resulted in overly optimistic predictions (some steroid patients remaining ambulant at implausible ages).
- Early > Late non-ambulatory: Exponential model with rate 0.25, as patients spend on average 4 years in each state [1].
- Late non-ambulatory > death: User-defined hazard function: linear increase in hazard until age 18, constant hazard of 0.143 until age 35 and then exponentially increased hazard by 15% each year [1].
- Only death from the late non-ambulatory state was assumed for simplicity and due to lack of available data (Fig. 1).

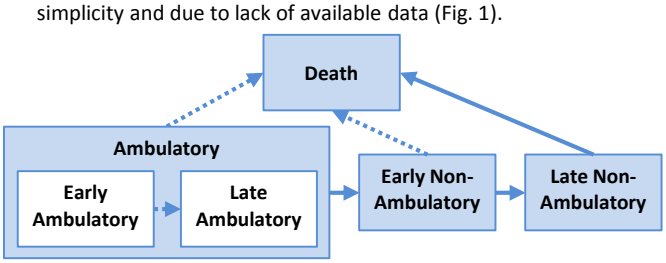
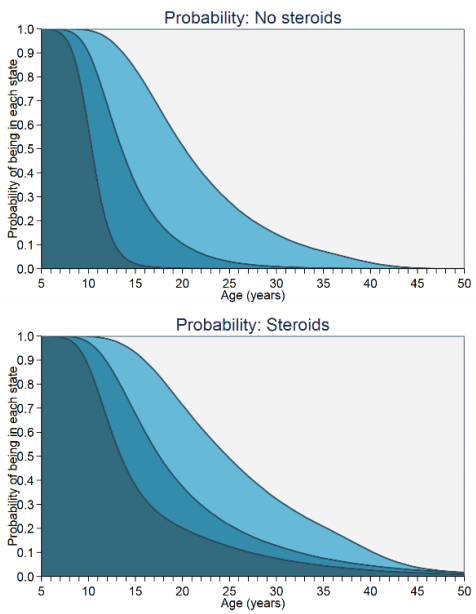


Figure 1: Illustration of the multi-state model fitted with health states: ambulatory, early non-ambulatory, late non-ambulatory and death. Dotted arrows represent transitions where there was insufficient data.

Data analysis: A Royston-Parmar model with two degrees of freedom, stratified by trial, was fit to the ambulatory > early non-ambulatory transition. Steroid use (yes/no) was included as a covariate for this transition only and the hazard of losing ambulation was 75% lower for steroid users. The probability of being ambulant at age 12 was 65% and 18% in the steroid users/non-users and of being alive at age 25 was 49% and 28% (Figs. 2,3). Fig. 4 shows the estimated restricted length of stay in each state. Extrapolating, a steroid user has an average life expectancy of 26.5 years, of which 16 years will be spent ambulant, 4 in the early non-ambulatory state and 6.5 in the late non-ambulatory state. Associated confidence intervals can be obtained for all predictions (not shown).



Figures 2 & 3: Probability of being in each state at different ages for non-steroid users (Fig. 2) and steroid users (Fig. 3).

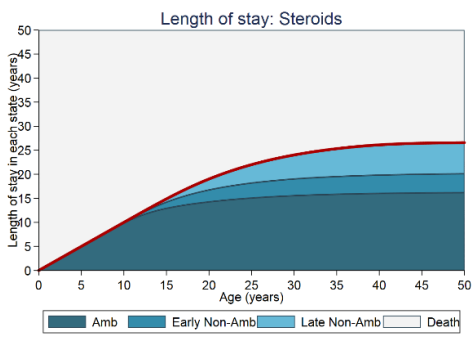


Figure 4: The expected duration spent in each state from birth. The red line indicates restricted mean life expectancy.

Conclusion

This study models the full natural history of DMD in a single unified analysis and highlights some of the challenges of working in a rare disease area. The results can be used to inform future economic decision models and identify where primary data collection or acquisition is required and is of particular value.

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