Research in Adult DMD

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Queen Square
What research is there?

• Medline search ‘Duchenne muscular dystrophy’
  – 3751 publications

• ‘AND Adult’ (4216334 publications)
  – 657 publications (most not on adult DMD)
  – 22/100 ‘pure’ adult DMD studies
  – Quality of life studies, carers burden, case series showing improved life expectancy (3/100)
  – biomarkers and outcome measures
  – Case reports (5/100)

• Clinical trials database (clinical trials.gov)
  – 167 studies
  – 14 include patients over 16 years
<table>
<thead>
<tr>
<th>Name of study</th>
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</thead>
<tbody>
<tr>
<td>Stem Cell Therapy in Duchenne Muscular Dystrophy</td>
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<tr>
<td>Research of Biomarkers in Duchenne Muscular Dystrophy Patients (IBISD)</td>
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<tr>
<td>Study Safety and Efficacy of BMMNC for the Patient With Duchenne Muscular Dystrophy</td>
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<tr>
<td>Open Label, Extension Study of PRO044 in Duchenne Muscular Dystrophy (DMD)</td>
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<tr>
<td>Eplerenone for Subclinical Cardiomyopathy in Duchenne Muscular Dystrophy (E-SCAR DMD)</td>
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<tr>
<td>Observational Study of Patients With Duchenne Muscular Dystrophy Theoretically Treatable With Exon 53 Skipping (pre U7-53)</td>
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<tr>
<td>Longitudinal Study of the Natural History of Duchenne Muscular Dystrophy (DMD)</td>
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<tr>
<td>Magnetic Resonance and Optical Imaging of Dystrophic and Damaged Muscle</td>
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<tr>
<td>Duchenne Muscular Dystrophy &lt; 18y in Norway: Genotype/Phenotype, Growth, Puberty, Bone Health and Quality of Life</td>
</tr>
<tr>
<td>2D Strain Evaluation: Children With Duchenne Muscular Dystrophy Versus Healthy Children</td>
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<tr>
<td><strong>Clinical Intramuscular Gene Transfer Trial of rAAVrh74.MCK.Micro-Dystrophin to Patients With Duchenne Muscular Dystrophy</strong></td>
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<tr>
<td>Therapeutic Potential for Aldosterone Inhibition in Duchenne Muscular Dystrophy</td>
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<tr>
<td><strong>Testosterone Therapy for Pubertal Delay in Duchenne Muscular Dystrophy</strong></td>
</tr>
<tr>
<td>Safety, Tolerability, and Pharmacokinetics of Single and Multiple Doses of HT-100 in Duchenne Muscular Dystrophy</td>
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</tbody>
</table>
New and growing population of people with DMD

Queen Square

Denmark 2012 survival to 47 years
Courtesy of Jes Rahbeck 2013
UK more children than adults with DMD (83% < 27 years)

Denmark 3x more adults than children, maximum age 47 years (44.2% < 27 years, over one third aged over 33 years)

- Courtesy of Dr Sunil Rodger Newcastle University (CARE NMD project)
Care-NMD survey

- Social inclusion in the UK much worse than other European countries
- Nearly 1/3 of adults not receiving recommended heart/lung checks
- Limited access to physiotherapy
- Adults are less likely to be satisfied with their care

‘Significant room for improving multidisciplinary care for this population in the UK’

Courtesy of Dr Sunil Rodger Newcastle University (CARE NMD project)
Accessible centres providing co-ordinated MDT care

Quinlivan, Matthews, Hanna: Current Opinion in Neurology 2014
Develop a network of centres of excellence for adults with DMD
North Star Network

- 17 participating centres
- 428/500 boys on data base had usable data
  - 396 steroid treated
  - 32 steroid naïve
  - 19 deflazacort
  - 15 alternate day
  - 154 10/10
  - 136 daily

Courtesy of Valeria Ricotti
## NorthStar Ambulatory Assessment

### Box 1 The 17 items of the NorthStar Ambulatory Assessment

- Stand
- Walk
- Stand up from chair
- Stand on right leg
- Stand on left leg
- Climb box step—right leg
- Climb box step—left leg
- Descend box step—right leg
- Descend box step—left leg
- Gets to sitting
- Rise from the floor
- Lift head
- Stand on heels
- Jump
- Hop—right leg
- Hop—left leg
- Run (10 m)
Age at Loss of Ambulation

Kaplan-Meier survival estimates

- Loss of ambulation:
  - Intermittent: 48/176
  - Daily: 36/165

- Median age of LOA:
  - Intermittent: 12 years
  - Daily: 14.5 years

Courtesy of Valeria Ricotti
Table 3  Moderate to severe side effects breakdown, $\chi^2$ analysis (intermittent prednisolone n=191; daily prednisolone n=169)

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Intermittent, n (%)</th>
<th>Daily, n (%)</th>
<th>$\chi^2$ p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temper tantrums</td>
<td>54 (28)</td>
<td>67 (40)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Mood swings</td>
<td>56 (29)</td>
<td>64 (38)</td>
<td>0.08</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>41 (21)</td>
<td>49 (29)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>29 (15)</td>
<td>39 (23)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Emotional liability</td>
<td>23 (12)</td>
<td>32 (19)</td>
<td>0.06</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (4)</td>
<td>19 (11)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Cushingoid features</td>
<td>28 (15)</td>
<td>56 (33)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>GI symptoms</td>
<td>12 (6)</td>
<td>23 (14)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>73 (38)</td>
<td>78 (46)</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (5)</td>
<td>38 (22)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>8 (4)</td>
<td>14 (8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Long bone fractures</td>
<td>13 (7)</td>
<td>9 (5)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMD z-score ≤ -2.5*</td>
<td>9 (5)</td>
<td>14 (8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cataracts</td>
<td>2 (1)</td>
<td>4 (2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>19 (10)</td>
<td>24 (14)</td>
<td>0.2</td>
</tr>
<tr>
<td>Easy bruising</td>
<td>5 (3)</td>
<td>7 (4)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*BMD z score=lumbar spine.
BMD, bone mineral density; GI, gastrointestinal.
DMD boys who started GC < 5 years of age

- N = 36, mean age = 4.56 y (SD = 0.39)
- The earliest starter = 3.42 years
- IP n = 17; DP n = 16; AD n = 3

DMD boys who started treatment ≥ 5 years

N = 222
Mean = 6.83 y (SD = 1.44)

Courtesy of Valeria Ricotti
DMD boys who started GC< 5 years of age

- Before age 7 (n=36): early starters increase by an extra 2.04 units NSAA per year
- P=0.04

Courtesy of Valeria Ricotti
Adult ‘North Star Network’

• Representatives from adult neurology centres met earlier this year at Queen Square
• A total of 650 adults with DMD were known to the group
• Need to develop centralised specialist Adult DMD services to co-ordinate care and develop research
• Standardised data collection
• Develop outcome measures
Important areas for research

- Transition (preparing people for adulthood)
- Natural history studies
- Outcome measures
- Quality of life and participation
- Physiotherapy/ hydrotherapy/ exercise
- Disease modifying therapies
  - Steroids, Exon skipping, Ataluren etc
- New technologies
  - Nano technology
  - Exo skeletons
OUTCOME MEASURES FOR NON AMBULANT DMD
Outcome measures: biomarkers

• Transcriptomics
• Proteomics
• Metabolomics
MRI Imaging

T₁ weighted MR Image with age and disease progression

Age 5
Age 6 -
Age 8 - 9
Age 10 - 11
Age 12 - 13
Age 14

Lee Sweeney: courtesy of PTC bio
Six minute walk test most validated clinical endpoint utilized in ambulatory DMD trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Endpoint</th>
</tr>
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<tbody>
<tr>
<td>2008</td>
<td>ataluren ‘007</td>
<td>6MWD</td>
</tr>
<tr>
<td>2010</td>
<td>drisapersen</td>
<td>6MWD</td>
</tr>
<tr>
<td>2013</td>
<td>tadalafil</td>
<td>6MWD</td>
</tr>
<tr>
<td>2013</td>
<td>ACT DMD</td>
<td>6MWD</td>
</tr>
<tr>
<td>2015</td>
<td>eteplirsen</td>
<td>6MWD</td>
</tr>
<tr>
<td>2015</td>
<td>Anti-myostatin</td>
<td>6MWD</td>
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Primary Endpoint: 6MWD

Secondary Endpoints:
- Time to 10% 6MWD Worsening
- 10-meter walk/run
- Stair climb
- Stair descend
- North Star Ambulatory Assessment
- PedsQL
- PODCI
- Myometry

Note: ataluren study conducted by PTC Therapeutics; drisapersen study conducted by GSK / Prosensa (Biomarin); tadalafil study conducted by Lilly; eteplirsen study conducted by Sarepta; anti-myostatin mAb study conducted by Pfizer.
Outcome reliability in non-ambulatory boys/men with Duchenne muscular dystrophy.
Connolly AM; Malkus EC; Mendell JR; Flanigan KM et al


Outcome measures: Clinically meaningful

- Respiratory Function
- EK scale
- Upper limb function
- Cardiac function
TRANSITION: PREPARING PEOPLE FOR ADULTHOOD
Health care behaviours in young adults with chronic disease

- Failure to engage with services/ non-attendance/ poor compliance
- Diabetes HbA1c worse
- Cancer outcomes improving slowest
- 50% of all psychiatric diagnoses emerge by 14 years and 75% by 24 years
- 1:10 18 year olds have depression
Biological Cognitive development

- Prefrontal cortex maturation
  - impulse control
  - planning
  - emotional regulation
Limbic system hypersensitive
- Continues into 3\textsuperscript{rd} decade
Transition to adulthood: 
Road Map for Adolescent Growth

Carl Pickhardt 2009

• Four stages
  – Stage 1 (9-13 years)
    • Letting childhood go
  – Stage 2 (13-15 years)
    • Forming a family of friends
  – Stage 3 (15-18 years)
    • Acting more grown up
  – Stage 4 (18-22 years)
    • Stepping off on one’s own
Becoming a Man

Life with Duchenne muscular dystrophy

Craig McLean, Liam McLean and David Abbott
New Technologies
What needs to change to develop adult DMD research in the UK?

- Engage patients
- Engage pharmaceutical companies
- Engage parents and carers
- Engage funding and regulatory bodies
- Develop a network of adult specialist centres
- Develop outcome measures and natural history data

Accessible Centres of excellence for adult DMD
Critical mass of patients
Summary

• Rapidly growing new population of adults with DMD
• There is an urgent need to develop centres of excellence co-ordinating multi-disciplinary care and build a ‘critical mass’ of patients
• Research needs to focus on natural history, quality of life, participation and outcome measures before therapeutic trials can be designed
• We need to engage funding and regulatory bodies