UNIVERSITY OF BIRMINGHAM

Literature Search on the Prevalence of Chronic Neurological Disorders

Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration

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For the Drivers Medical Group
DVLA
Swansea

ARIF

WMHTAC
West Midlands HTA Collaboration

About ARIF and the West Midlands Health Technology Assessment Collaboration

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively produce health technology assessments and systematic reviews. The majority of staff are based in the Department of Public Health and Epidemiology at the University of Birmingham. Other collaborators are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility at the University of Birmingham, pharmacists and methodologists from the Department of Medicines Management at Keele University and clinicians from hospitals and general practices across the West Midlands and wider.

WMHTAC produces systematic reviews, technology assessment reports and economic evaluations for the UK National Health Service's Health Technology Assessment (HTA) programme, the National Institute for Health and Clinical Excellence (NICE). Regional customers include Strategic Health Authorities, Primary Care Trusts and regional specialist units. WMHTAC also undertakes methodological research on evidence synthesis and provides training in systematic reviewing and health technology assessment.

The two core teams within WMHTAC are the Aggressive Research Intelligence Facility (ARIF) and the Birmingham Technology Assessment Group (BTAG)

ARIF provides a rapid on-demand evidence identification and appraisal service primarily to commissioners of health care. Its mission is to advance the use of evidence on the effects of health care and so improve public health. The rapid response is achieved by primarily relying on existing systematic reviews of research, such as those produced by the Cochrane Collaboration, the National Institute for Health and Clinical Excellence (NICE), the NHS Centre for Reviews and Dissemination, and the NHS Health Technology Assessment (HTA) programme. In some instances, longer answers to questions are required in which case mini rapid reviews of existing systematic reviews and key primary studies are compiled, typically taking 1-2 months to complete.

Occasionally a full systematic review is required and then topics are referred to BTAG who coordinate the production of systematic reviews for several customers under a number of contracts. ARIF is intrinsically involved in the production of these systematic reviews.

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1 Aims

The aim of this report was to provide information, and comment on:

- the UK prevalence and/or incidence of
    - Multiple Sclerosis
    - Motor Neurone Disease
    - Huntington's Disease (Chorea)
    - Muscular Dystrophy
- the prevalence and/or incidence of the above conditions by age, gender and condition-related subtypes

2 Background

For conditions that may affect a person's ability and fitness to drive, the DVLA currently relies on the completion of a drivers self-declaration form following initial diagnosis, and a self-assessment form for disease progression. Chronic neurological disorders such as Multiple Sclerosis (MS), Motor Neurone Disease (MND), Huntington's Disease (HD), and Muscular Dystrophy (MD) are characterised by a progressive loss of motor function and therefore require regular licensing reviews.

Multiple Sclerosis

The age of onset of MS is usually young and middle-aged adults.[1] The myelin sheaths surrounding the nerves of the brain and spinal cord breakdown causing an effect on nerve function. Symptoms are typically scattered depending on the area of the spinal cord and/or brain that is affected, but include an unsteady gait, ataxia (shaky movements of the limbs), nystagmus (abnormal eye movements), defects of speech and spastic weakness. Cognition and memory can also be affected. MS is characterised by recurrent relapses followed by remissions, although a small proportion of patients follow a chronic progressive course. The cause of MS is unknown.[1]

Motor Neurone Disease

MND is a rare disease with the average age of onset in middle age. Progressive degeneration of cells and nuclei in the brain, brainstem and spinal cord causes muscle weakness and wasting. Symptoms include spasticity, weakness, paralysis, and impairment of speech, swallowing and breathing. There are three main clinically distinct forms depending on the symptoms and area of the brain, brainstem or spinal cord affected: amyotrophic lateral sclerosis (ALS); progressive muscular atrophy; and progressive bulbar palsy. Other forms of MND exist but the definitions of these (and the three forms above) are not always clear or consistent. ALS accounts for 65-85% of all cases of MND.[2] There is no cure for ALS MND, which is usually fatal within 3 to 5 years. Inherited MND accounts for approximately 5% of cases but in all cases the exact cause is unknown.[3]

Huntington's Disease

The symptoms of Huntington's Disease appear in early middle age, although the underlying cause is the inheritance of a single gene defect.[4] Loss of neurones and cells in the cortex produce an unsteady gait, jerky involuntary movements (chorea), behaviour changes and progressive dementia. There is a juvenile subtype, which affects individuals in the second or third decade of life but only accounts for 10% of cases. The majority of individuals developing Huntington's disease are diagnosed between the ages of 30 and 60 with the highest diagnosis rate in the in the 50-60 year old age group. Mean survival after diagnosis is 15-20 years.

Muscular Dystrophy

MD refers to a group of genetically determined muscle diseases. There are numerous subtypes and classifications of the muscular dytrophies.[5] The most common forms of muscular dystrophy are Duchene muscular dystrophy (DMD), Myotonic dystrophy (MyD), Congenital muscular dystrophy (CMD), Emery – Dreifuss muscular dystrophy (EDMD), Limb girdle muscular dystrophy (LGMD), Becker muscular dystrophy (BMD) and Facioscapulohumeral dystrophy (FSHD). Affected muscle fibres progressively degenerate and are replaced by fatty tissue causing weakness and wasting. Classification has historically been made according to a set of symptoms, the age of onset, distribution of muscle weakness, progression of disease and mode of inheritance. Muscular dystrophies can be x-linked conditions or follow an autosomal dominant or recessive inheritance. The discovery of the MD genes has lead to reclassification according to the gene loci and protein product. The most common form of MD in the young is DMD, which is associated with a greater severity of abnormalities than BMD. Myotonic dystrophy is the most common form in adults.

Historically, the DVLA has accepted the information provided on the self-declaration/assessment forms as being an accurate description of the driver's physical and cognitive state and has not routinely required subsequent referral to a disability assessment centre. Recently, the DVLA has been requesting hospital letters from secondary care physicians treating MS patients, which is the disease accounting for the majority of those affected by the neurological disorders listed above. Comparison of the self-declaration form with the hospital letter has revealed a significant under-reporting of deterioration in function. The rate of disease progression of neurological disorders is highly variable making the frequency of licensing review difficult to ascertain. In addition, there may be under-reporting of the initial diagnosis, since the driving forum report seeing a lower than expected incidence of MS in drivers. This may be due to self-regulation of driving by MS sufferers and reduced occupation-related travel compared to healthy drivers.

Prevalence, incidence, rate of disease progression, and identification of risk factors are all important in guiding licence reviewing policy. This report aims to provide information on the prevalence and/or incidence of MS, MND, Huntington's Disease, and MD in the UK, and where evidence allows, a breakdown by age, gender and condition-related subtypes.

Further background information is given in the documentation supplied by the Drivers Medical Group contained in Section 7.1.

3 Methods

Outline methods were submitted to the Drivers Medical Group by email and acceptance subsequently confirmed by e-mail (Section 7.2).

In brief, searches were undertaken to identify studies reporting the prevalence and/or incidence of:

- Multiple Sclerosis
- Motor Neurone Disease
- Huntington's Disease
- Muscular Dystrophy

Prevalence and incidence information is best ascertained using cross-sectional and cohort studies. Therefore, in the first instance, searches focused on *reviews* of cohort and cross-sectional studies. When relevant reviews were not identified, or where only reviews with a weak methodology were found, a search for primary studies was employed.

The methodological quality of selected studies was assessed using standard criteria. Where possible, data on prevalence and incidence was extracted and tabulated. Prevalence and/or incidence for each condition was presented by age group, gender and condition-related subtypes where possible.

Searches and identification of data

MEDLINE (2000-2006), EMBASE (2000-2006) and the Cochrane Library (2006 Issue 3) were searched using the search strategies detailed in Section 7.3. In the first instance, searches were limited by date to publications from 2000 in order to access the most recent epidemiological data. In the absence of relevant reviews, searches were conducted for primary studies. If evidence was not available from primary studies the date restriction on searches was removed.

Initially we searched for robust UK based studies. This was extended to include studies involving populations of Northern Europe, then Northern Europe and USA, and finally, worldwide if necessary. Studies involving small populations thought not to be generalisable to the UK population were not selected.

Studies conducted in UK populations pre-2000 were considered more relevant than more recent studies conducted in non-UK populations.

Key words used in the search strategy covered all terms associated with each disease plus prevalence, incidence, cohort and cross-sectional study design terms (Section 7.3). Bibliographies of key articles were also checked for relevant articles.

A research analyst and an information specialist formulated the search strategy. Searches were undertaken by an information specialist. The information specialist and research analyst assessed the search results for relevant studies based on the title and abstract. Articles that adhered to the following broad criteria were obtained in full:

Design: Systematic reviews and/ or meta-analyses; primary studies (cohort studies or cross-sectional studies).

Population: General population from

- UK, or when not available,
- Northern Europe, or when not available,
- Northern Europe and USA,
- Worldwide.

Outcomes: Prevalence/incidence of MS/MND/Huntington's Disease/MD.

Exclusion: Studies conducted in a population with a very different ethnic mix to the UK, or in isolated communities from specific regions within a country thought not to be generalisable to the UK.

Full copy articles were assessed for their relevance to this report (external validity) and the most informative articles were examined further.

4 Results

4.1 Multiple Sclerosis

Searches identified one Health Technology Assessment (HTA) published in 2002, which reviewed existing epidemiology data for MS.[6] Two further reviews provided relevant information (Fox et al[7] and Pugliatti et al[8]). Together these three reviews provide a comprehensive up-to-date set of studies for MS prevalence and incidence across the UK.

The reviews highlight that uncertainties over the true prevalence and incidence of MS remain despite considerable efforts over many decades. The determination of prevalence is influenced by a number of key factors including how a case of the disease is defined. The criteria for a diagnosis of MS defined by Allison and Millar was used widely up to the mid-1980's.[9] This classed cases as 'probable MS' and 'early MS' cases, which introduced much ambiguity. With advances in diagnostic technology, a more rigorous definition, by Poser of 'definite MS' plus 'probable MS' cases was adopted.[10,11] More recently the McDonald criteria ('definite MS', 'possible MS', 'not MS') has been recommended by the International Panel in Multiple Sclerosis Diagnosis.[12] The review by Fox included a comparison of prevalence measured using both the Poser and McDonald criteria and found little difference between the two.[7] The review concluded that prevalence using a 'definite MS' diagnosis is more robust and that the earlier definition is now redundant. The Poser criteria has been used for most of the studies included in the three reviews.

Prevalence

The Health Technology Assessment (HTA) reported estimates of baseline prevalence of MS in England and Wales from studies published up to, and including, 1999. For this review, the most recent survey was used where more than one existed. The review has an underlying robust methodology and the identification of studies and inclusion criteria are aimed at ensuring quality. It is unlikely that the review has missed any MS prevalence studies in England and Wales up to 1999. This review was the best evidence available for this report.

The review by Pugliatti is a comprehensive review of the epidemiology of MS in Europe.[8] Where there was more than one study published, the review only included the most recent and largest populations. The Fox review reports the prevalence of MS in Devon in 2001 and provides a comparison with other surveys conducted in the UK.[7] Table 1 summarises the MS prevalence data extracted from the three reviews.

Table 1 MS prevalence data taken from the three reviews.[6-8]

Place (Study)	Year	Diagnostic criteria	Latitude	Cases	Study population	Prevalence per 100,000 (95% confidence intervals)
England						
Leeds (Ford et al, 1998)	1996	Poser	53.8°	522 [6] 712 [7]	732,061	72 (65-77) [6] 97 (90-105)*[8] 85 [7]
Rochdale (Shepherd et al, 1996)	1986	Poser	53.6°	232	207,600	112 (97-126)
North Cambridgeshire (Robertson et al, 1995)	1993	Poser	52.5°	401 [6] 449 [7]	378,959	107 (95-116) [6] 107 (98-118)*[7,8]
South Cambridgeshire (Robertson et al, 1996)	1993	Poser	52.2°	380	287,700	131 (119-145)
Suffolk (Lockyer, 1991)	1988	Allison and Millar	52.2°	58	31,379	185 (137-232)
Sutton Borough of London (Williams & McKeran, 1986)	1985	Allison and Millar	51.4°	176	170,000	104 (88-119)
Southampton (Roberts et al, 1991)	1987	Poser	50.9°	395 [6] 411 [7]	417,000 [6] 411,000 [7]	95 (85-104) [6] 95 (88-107) [7]
Sussex (Rice Oxley et al, 1995)	1991	Poser	50.8°	665	596,594 [6] 596,394 [7]	111 (103-120)
Devon (Fox et al, 2004)	2001	Poser	NR	402	341,796	118 (106-129) Adjusted to age and sex structure for Devon
Wales						
South East Wales (Swingler & Compston, 1988)	1988	Poser	51.7°	379 [6] 441 [7]	376,718	101 (90-111)
Scotland and Northern Ireland						
Eastern Scotland (Forbes et al, 1999)	1996	NR	NR	727	395,600	184 (171-198)
South East Scotland (Rothwell & Charlton, 1998)	1995	NR	NR	NR	864,300	187 (178-196)
Northern Ireland (McDonnell & Hawkins, 1998)	1996	NR	NR	288	151,000	168 (148-189)

NR not reported * Approx

The HTA reviewed nine studies conducted on populations from England and Wales (Table 1). The review by Pugliatti reported data from five UK studies. Three studies were conducted in Scotland and Northern Ireland, and two in England (Leeds and N Cambridgeshire) (Table 1). The Leeds and North

Cambrigeshire studies were common to both the HTA and Pugliatti reviews. The Fox review provided prevalence data from the Devonshire population. This data was not included in the HTA or Pugliatti reviews.

MS prevalence across England and Wales ranges from 72 to 185 in 100,000. The prevalence rate for Leeds is inconsistent between the three reviews 72 vs 85 vs 97 per 100,000. It is not clear why this data should differ and requires scrutiny of the original article, which is beyond the scope of this report. Prevalence for Scotland and Northern Ireland (168 to 187 per 100,000) is almost double that seen in some studies from England and Wales. The time period studied ranged from 1985 to 2001. Most of the studies were conducted over a decade ago and it is uncertain what this may mean for predicting current prevalence rates. Study population size varies considerably. The Suffolk study was the smallest, with the studies in Leeds and in SE Scotland the largest. Details of study design (cross-sectional survey, cohort, registry data) and methodology was not generally reported by the reviews. Age- and sex-standardised prevalence rates were not reported in the reviews, which makes comparison of prevalence rates between studies difficult due to the inherent differences in the structure of the different study populations involved.

An average prevalence of MS in England and Wales for an average year was reported by the HTA for the nine studies reviewed. This was calculated with and without the Leeds data (Table 2). The prevalence of 72 per 100,000 reported in the Leeds population by the HTA was low compared to the other studies and yet had a significant effect on the average because the population was comparatively large. Including the Leeds data gave an average prevalence of 100 per 100,000 (95% CI 97-104) whereas excluding the Leeds data gave a prevalence of 109 per 100,000 (95% CI 105-113).

Table 2 Average prevalence for nine studies in England and Wales reported by the HTA.[6]

	Year	**Latitude**	**Cases**	**Study population**	**Prevalence per 100,000 (95% confidence intervals)**
Average including Leeds data	1989.5	52.2°	3208	3,198,011	100 (97-104)
Average excluding Leeds data	1991	51.7°	2686	2,465,950	109 (105-113)

The HTA also reported the prevalence of MS in an English population of 3,617,890 from a General Practice Research Database in 1991 as 102 (98-105) in 100,000 (with 3677 cases).

Prevalence by gender and age

The HTA report does not provide prevalence or incidence broken down into age, gender or MS subgroups. Pugliatti reports prevalence data broken down by gender and age. Table 3 shows prevalence of MS in the UK by gender. MS is over twice as common in women than in men in the UK.

Table 3 Prevalence per 100,000 of MS in the UK by gender.[8]

Place (Study)	Previous year	Prevalence Women (95% confidence intervals)	Prevalence Men (95% confidence intervals)	Women: Men ratio
Eastern Scotland (Forbes et al, 1999)	1996	262 (241-285)	100 (86-115)	2.8
South East Scotland (Rothwell & Charlton, 1998)	1995	257 (242-272)	112 (102-122)	2.5
Northern Ireland (McDonnell & Hawkins, 1998)	1996	230 (NR)	104 (NR)	2.3
Leeds (Ford et al, 1998)	1996	141 (NR)	52 (NR)	2.8
North Cambridgeshire (Robertson et al, 1995)	1993	NR	NR	2.2

NR not reported

MS prevalence broken down by age in the UK is presented in Table 4. MS prevalence is greatest in 50-64 year olds, except in Eastern Scotland where there are more prevalent cases in the 35-49 year old group. This is more consistent with data from other European countries where the highest prevalence rates are seen in the 35-49 year olds.[8] A comparison of age-related prevalence between the studies is confounded by the use of different age subgroups and a lack of reporting of crude prevalence rates, therefore caution must be exercised in interpreting and discussing this data.

Table 4 Prevalence per 100,000 of MS in the UK by age.[8]

Place (Study)	Previous year	Age (years)					
		0-17	18-34	35-49	50-64	65-74	75+
Eastern Scotland (Forbes et al, 1999)	1996	4	91	383	358	176	89
South East Scotland (Rothwell & Charlton, 1998)	1995	7	97	356	363	261	103
Northern Ireland (McDonnell & Hawkins, 1998)	1996	4	81	343	377	313	60
Leeds (Ford et al, 1998)	1996	NR	15-70*	150-250*	200-250*	150*	60*
North Cambridgeshire (Robertson et al, 1995)	1993	NR	10-75*	200-300*	250-300*	170*	75*

NR not reported *Approx

The review by Fox did not provide full details of prevalence broken down by gender and age in the Devon population but the highest MS prevalence for women was seen in the 45 to 54 year old age group (370 per 100,000) and for men in the 55 to 64 year old group (207 per 100,000).

Prevalence by disease subtype

Pugliatti reported the proportion of MS cases broken down by disease course.[8] The *average* estimated proportion of MS cases by disease course based on the prevalence in the UK was calculated to be 45% relapsing-progressive combined with secondary progressive, 40% relapsing-remitting, and 15% primary progressive MS. Categorisation of MS varies between studies with some phases being combined with others and some phases being omitted entirely. Case assessment in hospital settings may lead to an overestimation of the progressive forms whereas the proportion of progressive disease may have been underestimated by the need to use prevalence rates taken at one point in time, as this does not take into account future outcomes (relapsing-remitting MS becoming secondary progressive MS). These percentages are, therefore, a best estimate. A breakdown by study is shown in Table 5.

Table 5 Proportion of MS patients (%) by disease course in the UK.[8]

Place (Study)	Year	Relapsing-Remitting MS (%)	Relapsing-Progressive combined with Secondary-Progressive MS (%)	Primary Progressive MS (%)
Northern Ireland (McDonnell & Hawkins, 1998)	1996	48	40	12
Leeds (Ford et al, 1998)	1996	38	47	15
North Cambridgeshire (Robertson et al, 1995)	1993	55	23	22

Fox reported a breakdown of prevalence by disease course in the Devon population. 46% of prevalent cases were in the relapsing-remitting course, 30% in secondary progressive and 12% in primary progressive MS. Clinically isolated syndromes and unknown accounted for 9% and 3% of cases respectively.

The severity of disability due to MS can be measured using disability status scores. The Kurtzke's Expanded Disability Status Score (EDSS) has been adopted for MS.[13] Functional neurological systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other) are measured by assigning a score to each. Scores range from 0 (fully ambulatory) to 10 (death due to MS). An EDSS score of 0-3.5 indicates fully ambulatory with moderate disability in one or more functional systems, 4.0-6.5 refers to fully ambulatory but severe disability, and 7.0-9.5 indicates a requirement for wheelchair use, confinement to bed and totally dependent. A Northern Ireland study (reviewed by Pugliatti) showed prevalence by EDSS scores of 32.5% for 0-3.5, 47.5% for 4.0-6.5, and 20% for a score of 7.0-9.5.[8]

Geography of MS

All three reviews comment on the south to north increasing gradient in MS prevalence seen in the UK. Worldwide MS prevalence tends to be greater in the latitudes closer to the poles than those near the equator. Whether this is a true reflection of environmental or genetic factors is uncertain and this applies equally to the UK. As noted earlier, comparison between studies is confounded by differences

in study design and methodology but the data in Table 1 seem to show a difference in prevalence between the populations in Scotland and Northern Ireland and those in the south of England and Wales. Table 6 shows estimates of prevalence by latitude taken from the HTA report.

Table 6 Estimates of MS prevalence by latitude in the year 2000.[6]

	South Coast Latitude 50.00°	**Scottish Borders Latitude 55.75°**
Prevalence with Leeds data	92 per 100,000	137 per 100,000
Prevalence without Leeds data	104 per 100,000	155 per 100,000

Incidence

Incidence rates for MS were not widely reported by the three reviews.

The review by Pugliatti presented a crude total annual incidence rate for Scotland and North Cambridgeshire (Table 7). An incidence of twelve new cases of MS per 100,000 per year in Scotland during the period 1992-1995 was significantly higher than that reported for North Cambridgeshire.

Table 7 Crude total incidence rate (per 100,000 per year) of MS in the UK.[8]

Place (Study)	**Time period**	**Study population (ca.)**	**Rate (95% confidence interval)**
South East Scotland (Rothwell & Charlton, 1998)	1992-1995	379,000	12.0 (10.6-13.3)
North Cambridgeshire (Robertson et al, 1995)	1990-1995	864,000	4.8 (3.8-6.0)

The HTA report presented estimates of prevalence and incidence (prevalence/ mean survival) of MS for England and Wales for the year 2000 (Table 8).

Table 8 Estimates of MS prevalence and incidence in England and Wales in the year 2000.[6]

	With Leeds data	**Without Leeds data**
Prevalence	107 per 100,000	117 per 100,000
Incidence	3.5 per 100,000	3.8 per 100,000

Incidence by gender and age

There was no data available on incidence broken down by gender and age.

Incidence by disease subtype

There was no data provided on incidence broken down by disease subtype.

Summary

There are several limitations of the data presented above. Sampling bias affects most prevalence and incidence type studies since it is impossible to measure the prevalence of a disease in the whole population of interest. A sample of the population has to be used, which may not be representative of

the whole population. Sampling a larger proportion of the population of interest reduces this bias. Case identification is also important. Not all of the eligible individuals may be identified and included in an analysis. Even the most intensive of surveys collecting data from registries, using a range of sources may miss cases. Most of the studies reviewed by the HTA report have used neurology clinic and GP records but these may not be comprehensive. The HTA report did not use a method ('capture-recapture') to estimate missed cases but suggest that it is somewhere between 10 and 20%. These will largely be those less severe cases. Fox attempted to capture all cases in the Devonshire population by chasing all sources of information and using the capture-recapture method to estimate the number of missed cases. A high coverage with few missed cases was reported.

Comparison between studies needs to be treated with caution. Prevalence rates tend to be higher where MS awareness is greater, survey methods are more accurate, and where studies are conducted repeatedly over time. These factors are likely to differ between studies. Other differences in methodology between studies include those relating to diagnostic criteria, case finding, categorisation (by age, disease severity and course), survey setting, and the study design (use of nationwide cross-sectional surveys or registries).

In summary, three good reviews, one of which is of a very high quality, report the major studies for the prevalence/incidence of MS in UK populations. Generalisability of the prevalence data presented above to the general populations of interest to the DVLA may not, therefore, be an issue for MS. The quality of the studies themselves is harder to assess since full details were not given in the reviews. An assessment of the original studies was beyond the scope of this report. The prevalence of MS for England and Wales was generally reported as more than 100 in 100,000 while that for Scotland and Northern Ireland is much higher. MS is twice as common in women than men and appears to be more prevalent in the 50-64 year old age group in the UK. Data on MS disease subgroups is limited. As technology for the diagnosis of MS has advanced so the criteria for the classification of MS has evolved making prevalence studies more robust but other methodological differences make comparison between studies difficult.

4.2 Motor Neurone Disease

Only one relevant review for MND (Worms et al) was identified by our searches.[14] In this review the epidemiology of MND in Europe and North America was reviewed for the 1990's. This review searched for studies based on keywords in 2000 in MEDLINE, EMBASE, and two other databases. Only one study in a UK population (Mitchell et al, 1998) was identified by this review. The study was conducted over the period 1989-1993 in Lancashire and South Cumbria with a study population size of 1,473,000. Cases were defined using diagnostic criteria for MND (clinical signs and an electromyogram). Most of the other European and North American studies reviewed by Worms report the prevalence of ALS using the El Escorial criteria. This is an internationally agreed set of diagnostic criteria for MND published in 1994.[15]

Prevalence

There was no prevalence study for the UK in the 1990's reviewed by Worms. Five studies (Italy, Ireland and Canada), using a diagnosis of either ALS or MND and a mixture of diagnostic criteria, show a range of prevalence for the 1990's of 2.7 to 7.4 per 100,000. The average being 5.2 per 100,000, which is close to the UK prevalence suggested by another source.[2]

Prevalence by gender and age

There was no data available on prevalence broken down by gender or age in the review by Worms.

Prevalence by disease subtype

The male:female ratio for prevalence in Canada was 1.5. There was no other data provided on prevalence broken down by disease subtype.

Incidence

Worms calculated the average yearly incidence from crude data giving an incidence of MND in Lancashire and South Cumbria of 1.76 per 100,000 per year for the 1990's decade. Twelve studies in Europe (Italy, France, Ireland, UK) and three in North America (USA) were analysed altogether to give a range of incidence for ALS of 1.47 to 2.70 per 100,000 per year for the 1990's decade (average 1.89 in 100,000).

Incidence by gender and age

There was no incidence data by gender and age for the UK. The average male:female ratio was 1.3 across the European and North American studies. The incidence of MND/ALS rises with age. Worms presents a crude estimate of the incidence of MND/ALS broken down by age and averaged across the European and North American countries studied for the 1990's. The 25-34 year old age group shows an incidence of 0.4 per 100,000; 0.8 per 100,000 in 35-44 year olds; 2.9 per 100,000 in 45-54 year olds; 6.2 per 100,000 in 55-64 year olds; 9.0 per 100,000 in 65-74 year olds; and 6.5 per 100,000 in the over 75 year olds.

Incidence by disease subtype

There was no data on incidence broken down by disease subtype.

Summary

Recent UK MND/ALS prevalence and incidence data from reviews was limited and the review by Worms only reported one UK study (conducted 1989-1993). The average prevalence and incidence for Europe and North America was 5.2 and 1.89 per 100,000 respectively for studies reviewed by Worms.[14] The European and North American data probably serves as a good approximation for the UK population since the general ethnicity and population structure of the countries reviewed by Worms does not differ widely from the UK.

4.3 Huntington's Disease

Two reviews were identified that contained information on the incidence and prevalence of Huntington disease in the UK.[16 17]

The first is a systematic review of the prevalence of Huntington's disease (Al-Jader et al), which was conducted in order to establish the Frequency of Inherited Disorders Database (FIDD), which is maintained by the University of Cardiff (www.uwcm.ac.uk/uwcm/mg/fidd/).[16] It is a record of the incidence and prevalence of inherited conditions and was published in 2001 and contains the results of searches of MEDLINE from 1966-2001. The review identified 100 relevant articles, the majority of which were published in the 1980's. Data from the UK studies have been extracted and included in Tables 9 and 10. The studies that have been included in FIDD are subject to inclusion criteria including ascertainment, selection bias and diagnosis method of included populations. The author of the review was contacted to confirm the inclusion criteria and details of quality assessment of studies (Dr Al-Jader personal communication). Therefore the individual studies have not been scrutinised further for this report.

The second review identified is a narrative review (Harper) that reports on the epidemiology of Huntington's disease in the UK.[17] This review contained many of the studies identified in the Al-Jader review, but also included some unpublished data obtained by the author from genetic registers. This data was collected in 1987 and was for regions in the South of England including Cornwall, Devon and Wessex. This data has also been added to Tables 9 and 10.

Prevalence

Table 9 The Prevalence of Huntington's disease in the UK.[16 17]

Place (Study)	Year	Cases	Study population	Prevalence per 100,000
England				
East Anglia (Caro 1977)	1971	54	584,415	9.2
Northamptonshire (Reid 1960)	1967-1968	27	428,000	6.3
Carlisle (Brewis et al 1966)	1961	2	71,101	2.8
Essex (Heathfield 1967)	1965	81	3,271,000	4.5
Oxford (Shiwach & Lindenbaum 1990)	1985	138	2,437,300	5.6
Cornwall*	1987	22	453,100	4.8
Devon*	1987	46	1,010,000	2.5
Wessex*	1987	92	2,457,473	2.5
Wales				
North (Quarrell et al 1988)	1950	19	340,941	5.5
South Gwent (Walker et al 1981)	1981	131	1,720,901	7.6
South (MacMillan & Harper 1991)	1991	79	939,300	8.4
Northern Ireland				
Northern Ireland (Morrison et al 1995)	1991	101	1,569,971	6.4
County Donegal (Morrison & Nevin 1993)	1991	2	128,117	1.6

Scotland				
West (Bolt 1970)	1960	154	2,959,600	5.2
Grampion, North East (Simpson & Johnston 1989)	1984	47	462,981	9.9

* data from genetic registers[17]

Prevalence (Table 9) was found to range from 1.6- 9.9 per 100,000. The population sizes studied ranged from 128,117 in County Donegal to 3,271,000 in Essex. The difference in prevalence between these studies was 1.6 in County Donegal and 4.5 in Essex. An average prevalence of Huntington's disease calculated from the data in Table 9 gives 5.5 per 100,000 (1950-1991). Most of this data is pre-1990 and therefore its relevance to the current population is unclear.

Prevalence by gender and age

There was no information available on the breakdown of prevalence by gender and age.

Incidence

Incidence data was hard to find. It is difficult to collect incidence data for late onset conditions such as Huntington's disease, because it relies on accurate early diagnosis and early symptoms may be missed or not recalled by patients. As shown in Table 10, the incidence appears to be between 5.5 - 7.5 per 100,000, with the exception of the Scottish study as this was in a small and isolated population with an unusually high incidence. However, these studies are now quite old and this data should be interpreted with caution since the modern population is likely to differ from those studied.

Table 10 The Incidence of Huntington's disease in the UK.[16]

Place (Study)	Year	Cases	Population	Incidence per 100,000 per year
England				
Bedfordshire (Heathfield & Mackenzie 1971)	1965	30	427,970	7.5
Cornwall (Bickford & Ellison 1953)	1953	NR	NR	5.5
Moray Firth (Lyon 1962)	1962	5	896	558

NR not reported

Incidence by gender and age

There was no information on the incidence broken down by gender and age.

Summary

The available data from the UK suggests the prevalence of Huntington's disease is between 1.6- 9.9 per 100,000 (average 5.5 per 100,000). Incidence data was harder to find and the studies generally data pre-1970.

Incidence is difficult to measure in diseases with a late onset and the amount of available information reflects this. The available data suggests incidence is between 3.5-5.5 per 100,000 per year. The

breakdown of prevalence or incidence by age, gender and ethnicity was not found, but data on age at diagnosis confirms the late-onset of this condition, with the majority of individuals diagnosed between the ages of 50-60 years.

4.4 Muscular Dystrophies

No relevant reviews of the prevalence and incidence of muscular dystrophy were identified. Four primary studies were identified that gave useful information on the incidence and prevalence of neuromuscular disorders in the UK.[18-21] The first is a study of the prevalence of inherited diseases from Northern Ireland (Hughes et al).[19] The second is by MacMillan & Harper carried out on a population in South Wales.[18] The third is a study of DMD in the West Midlands (Bundey).[20] Lastly a study of the worldwide prevalence of neuromuscular disorders was also identified (Emery) [21], which contained some useful information on UK prevalence. The FIDD also provided prevalence data for MD. All data has been extracted and summarised in Table 11.

Prevalence

Due to the nature of muscular dystrophies, prevalence is presented by subtype. Prevalence data was available for most of the major subtypes of the muscular dystrophies and is summarised in Table 11.

Table 11 The prevalence of muscular dystrophies in the UK.[18-21]

Condition	Place (Study)	Year	Cases	Study population	Prevalence per 100,000 (95% confidence intervals)
Myotonic Dystrophy (MyD)	South Wales (MacMillan & Harper, 1991)[18]	1973-1989	NR	939,300	7.1 (5.5-9.1)
	Northern Ireland (Hughes et al, 1996) [19]	1993-1994	188	1,573,282	11.9 (NR)
Duchene Muscular dystrophy (DMD)	South Wales (MacMillan & Harper, 1991)[18]	1973-1989	NR	939,300	4.7 (3.4-6.3)
Facioscapulo-humeral dystrophy (FSHMD)	North East England (FIDD)	1955	22	2,000,000	1.1 (NR)
	Wales (FIDD)	1989	56	2,800,000	2.0 (NR)
	South Wales (MacMillan & Harper, 1991)[18]	1973-1989	NR	939,300	2.9 (1.9-4.1)
	Northern Ireland (Hughes et al, 1996) [19]	1993-1994	50	1,573,282	3.1 (NR)
Becker muscular dystrophy (BMD)	Northern England (FIDD)	1988	73	3,070,000	2.3 (NR)
	South Wales (MacMillan & Harper, 1991)[18]	1973-1989	NR	939,300	5.0 (3.2-7.6)

	Northern Ireland (Hughes et al, 1996) [19]	1993-1994	25	1,573,282	1.5 (NR)
Limb Girdle muscular dystrophy (LGMD)	North East England (FIDD) Scotland, Edinburgh (FIDD) Northern Ireland (Hughes et al, 1996) [19]	1988 1979 1993-1994	4 10 18	3,070,000 750,728 1,573,282	0.13 (NR) 1.3 (NR) 1.1 (NR)
Congenital muscular dystrophy (CMD)	Northern Ireland (Hughes et al, 1996) [19]	1993-1994	9	1,573,282	0.5 (NR)
Emery-Dreifuss muscular dystrophy (EDMD)	Northern Ireland (Hughes et al, 1996) [19]	1993-1994	7	1,573,282	0.4 (NR)

NR not reported

Myotonic dystrophy is one of the most prevalent muscular dystrophies worldwide.[21] The prevalence data from the UK reflects this, with the highest prevalence being found in this subgroup. Prevalence ranged from 7.1- 11.9 per 100,000.

For DMD the only available evidence is from South Wales and estimates the prevalence to be 4.7 per 100,000 (95% confidence intervals 3.4- 6.3 per 100,000).

FSHMD is a common muscular dystrophy but its prevalence may be higher than indicated as some mild cases may go unnoticed. [22] There is a great deal of variation in the worldwide estimate of prevalence of FSHMD, which ranges from 2.2- 66.9 per 100,000.[21] The data identified from the UK was at the lower end of the worldwide estimate and ranged from 1.1-3.1 per 100,000.

BMD ranged in prevalence from 1.3- 5.0 per 100,000 in the studies identified. BMD is difficult to distinguish from LGMD on the basis of symptoms, so studies conducted prior to advances in molecular techniques should have the method of diagnosis evaluated. The studies reporting data from the late 1980's and early 1990's have lower prevalence rates than the study which spans 1973-1989 (1.3- 2.3 per 100,000 versus 5.0 per 100,000 respectively).

LGMD was one of the less prevalent conditions ranging from 0.13 – 1.3 per 100,000 in the studies identified.

There was a lack of information available for the prevalence of CMD in the UK. CMD is a complex condition as it is difficult to diagnose and has a number of different forms.[22] Worldwide prevalence suggests CMD is quite common with an estimated prevalence of 10 per 100,000.[21] The only data identified for the UK was from Northern Ireland where the prevalence was 6 per 100,000.[19]

There was a lack of information on the prevalence of EDMD in the UK. The prevalence in Northern Ireland was 0.4 per 100,000.[19] The European prevalence of EDMD has been estimated to be 1-2 per 100,000, but the origin of this estimate is unclear.[22]

Prevalence by gender and age

The study by MacMillan and Harper gives data broken down by gender and age with prevalence of 9.6 per 100,000 in males and 21 per 100,00 in males under the age of 30.[18] No other data by age was given in this or any of the other studies.

Incidence

Incidence is presented by disease subtype. Some incidence data was found for DMD, BMD and FSHD in the UK and is shown in Table 12. The data comes from studies undertaken from 1966-1989, so there is a lack of up to date information for the UK. The overall range in incidence for the condition where information was available ranged from 0.5- 34.7 per 100,000 per year.

Table 12 The incidence of muscular dystrophies in the UK.

Condition	Place (Study)	Year	Cases	Study population	Incidence per 100,000 per year (95% confidence intervals)
Duchene muscular dystrophy (DMD)	Northern England (FIDD)	1988	76	3,070,000	2.4 (NR)
	England, Birmingham* (Bundey, 1981) [20]	1979-1980	27	10,434	24.4 (NR)
	South Wales (MacMillan & Harper, 1991)[18]	1973-1989	NR	939,300	34.7 (24.5-47.9)
Becker muscular dystrophy (BMD)	Northern England (FIDD)	1988	43	737,662	5.8 (NR)
	Oxford (FIDD)	1966	5	875,000	0.6 (NR)
	South and Mid Wales (MacMillan & Harper, 1991)[18]	1988	23	939,300	2.4 (NR)
	Scotland, Edinburgh (FIDD)	1979	5	750,728	0.66 (NR)
Facioscapulo-humeral dystrophy (FSHMD)	Wales (FIDD)	1989	71	2,800,001	2.5 (NR)

NR not reported * population boys aged 5-16

DMD had the highest incidence with a range from 2.4- 34.7 per 100,000 per year. The incidence was lowest in Northern Ireland, which had the largest population sample. The study in Birmingham only

included boys of school age (5-16 years). The incidence of BMD ranged from 0.6-5.8 per 100,000 per year. The lower figures where found in Oxford and Edinburgh. These two studies were the oldest of the identified studies. The only other incidence data found was for FSHMD, which was from a large study in Wales with a 2.8 million population. The incidence of FSHMD was found to be 2.5 per 100,000 per year. The information on incidence is from studies pre-1990 so its relevance to modern populations is unclear.

Incidence by gender and age

There was a lack of incidence data broken down by gender and age. Table 12 shows a prevalence of 24.4 in boys aged 5-16 years in a Birmingham population.

Summary

The muscular dystrophies are a group of conditions that have become much better classified since the advent of, and advances in, molecular genetics. There are a range and number of subtypes of muscular dystrophies, which makes general incidence and prevalence information quite difficult to find and interpret. This is reflected in the range of values found in worldwide prevalence.[21] The studies by Hughes[19] in Northern Ireland and MacMillan & Harper[18] in South Wales represent the best information available for the prevalence of muscular dystrophies in the UK. Incidence data was very hard to find and patchy in its representation of the conditions and subtypes. For both prevalence and incidence there is a lack of up to date information.

5 Conclusions

Evidence for the prevalence of MS in UK populations is widely available. We identified three recently published good reviews that are likely to have identified most, if not all, of the studies conducted in UK populations.[6 7 8] Prevalence in the UK is estimated to be more than 100 per 100,000 with an estimated incidence of 3.5 to 3.8 per 100,000 for the year 2000. MS is more than twice as likely to occur in women than men and is more prevalent in the 50-64 year old age group. Comparison between studies is confounded by difference in study methodology.

Evidence for MND was harder to find. Only one review focusing on European and North American studies was identified.[14] One study in a large UK population in 1989-1993 was reported by this review, but this study did not provide UK specific prevalence data. The average prevalence (1990's) for the Europe and North America studies in the review was 5.2 per 100,000. The incidence of MND in the UK was 1.76 per 100,000 per year for the 1990's decade. The range of incidence for ALS across the 15 European and North American studies was 1.5 to 2.7 per 100,000 per year (average 1.89 in 100,000). The average male:female ratio was 1.3. The incidence of MND/ALS rises with age and is highest in 65-74 year olds (9.0 per 100,000).

Evidence on the prevalence of Huntington's disease was found in the report of the setting up of the Frequency of Inherited Disorders Database.[16] This useful resource was maintained until 2001. Prevalence of Huntington's disease ranged from 1.6 to 9.9 per 100,000 reported by the studies contained in this database. Information on incidence is more difficult to obtain due to the late onset of disease and problems with accurate diagnosis date. With the exception of one study with very high incidence in Scotland, incidence ranged from 5.5 to 7.5 per 100,000 per year from the two studies in the FIDD. However, these studies were quite old so the results should be interpreted with caution.

Evidence on MD is complicated by the number of conditions within this group of disorders and the numerous subtypes of each condition. There are two good studies looking at a number of muscular dystrophies and other neuromuscular disorders in South Wales and Northern Ireland (published in 1991 and 1996 respectively).[18 19] From these studies, and others contained in the FIDD, incidence and prevalence for the major types of MD have been estimated. The majority of studies are now quite old so relevance to the modern population could be questioned. More accurate molecular diagnosis has become available since the 1990's.

5.1 Limitations

This is not a systematic review but a rapid assessment of the relevant literature. Although the search strategies were broad and comprehensive for both systematic reviews and primary studies, the searches for primary studies were restricted to cohort and cross-sectional studies assessing prevalence and incidence.

Cohort and cross-sectional studies are inherently open to sampling bias due to the possibility of non-representative sampling. There are several factors that may lead to non-representative sampling, one of which is how cases are identified and classified. Over time case identification and classification criteria have changed for the disorders considered in this report. Study setting may also affect whether cases are identified or missed. Study methodology and the frequency of study for the population of interest may be different between studies and has also changed over time. These issues make a comparison between studies difficult.

Availability of UK data was often limited, making extrapolation from other populations necessary. Where possible, populations from European and North American countries were used, which have a similar ethnicity, gender and age structure to that seen in the UK. We also found a lack of recent data, which required the use of older studies of prevalence and incidence. It is not clear how the populations under study have changed over time, and whether the prevalence and incidence of the disorders considered in this report have been affected by this. This type of analysis is beyond the scope of this report.

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7 Appendices

7.1 Details of Request

ARIF REQUEST FORM

Date of Request 25 / 08 / 06

Lead Medical Adviser Issuing request

Name – Dr H Major
Senior Medical Adviser

Contact details

Drivers Medical Group
DVLA
Sandringham Park
Swansea Vale
Llansamlet
Swansea
SA7 OAA

1. Without worrying about the structure of the question, state in full the nature and context of the problem.

A) We need to know the prevalence of:

1. MS
2. Motor Neurone Disease
3. Huntington's Disease
4. Muscular Dystrophy

B) For each of the conditions by:-

1. age group
2. gender
3. the age-related incidents of diagnosis and mortality rates

C) Are we able to identify low risk people in each condition for whom regular licensing review is not required?

D) Are we able to identify high risk people in condition for whom there is a rapid decline and regular review is required?

E) Identify those for whom we can accept self-declaration of continuing fitness based on the CN1 form (attached) and who will be subject to a 2 or 3 year review.

E) Identify those for whom a til 70 licence can be acceptable and for all conditions.

G) Identify key morbidity features which indicate decline of the condition specific for driving, cognitive and limb particularly.

H) It would also be helpful if we could have some information on the diagnostic criteria and Investigations for each of the conditions and the assessment tools/indicators used in Measuring deterioration/progression.

2. Please give a background to the question. Why has DMG raised this problem?

We need to know the rate of decline for each condition and the principle morbidity, specifically limb disabilities, cognitive and/or both.

3. Giving references where appropriate, briefly detail the sources you have used to obtain background information on the *options* and *issues*, which might be important for the problems, you describe.

(a) Chapter 1 Chronic Neurological Disorders – At a Glance guide to the current Medical Standards of Fitness to Drive February 2006.

(b) McDonald W.I., Compston A., et al (2001) "Recommended Diagnostic Criteria for Multiple Sclerosis" Annual of Neurology, Vol 50, Issue, P.121-127.

(c) Confavreux C., Vukusic S., et al (2000) "Relapses and Progression of Disability in Multiple Sclerosis": The New England Journal of Medicine, Vol 343, Number 20, p1430-1438.

(d) Compston A., Coles A., "Multiple Sclerosis": The Lancet, Vol 359:p1221-31

(e) Charlton J., Koppel S., et al (2004) "Influence of Chronic Illness on Crash Involvement of Motor Vehicle Drivers": Monash University Accident Research Centre, Report No 213:p241-249

(f) CN 1 form (DVLA form)

4. Please give name and contact details of any expert or clinical contact e.g. relevant Panel Chairman/expert Panel member.

Dr Philip E M Smith
MD FRCP
Consultant Neurologist
University Hospital of Wales
Heath Park
Cardiff
CF14 4XW

[redacted]

[redacted]

5. What is the nature of the target population of the issue detailed above? E.g. age, profile, vocational drivers, young drivers, other co-morbid features.

Group 1 drivers, rarely Group 2, but can the low risk of progression be identified?

6. What are the outcomes you consider particularly important in relation to the question posed? What decisions rest on these outcomes?

To identify the rate of decline of each of the conditions and the likely frequency of licensing review

What is the latest date that an ARIF response would be of value | 27 / 10 / 06 |

Please either:

Fax this form to: 0121 414 7878 marking FAO ARIF

E-mail as a word document or pdf attachment to: [redacted]

Post to:- **Dr David Moore**
Senior Research Reviewer and Analyst
Aggressive Research Intelligence Facility
West Midlands Health Technology Assessment Collaboration
Department of Public Health
University of Birmingham
Edgbaston
Birmingham
B15 2TT

Please ring 0121 414 3166 or 6767 if you have any queries, or you want to check the progress with your request.

7.2 Outline methods

This report will provide information on the prevalence and/ or incidence of:

- Multiple Sclerosis
- Motor Neurone Disease
- Huntington's Disease
- Muscular Dystrophy

Where possible, prevalence for each condition will be broken down into age group, gender and any condition-related subtypes.

We will identify studies likely to provide this information by searching MEDLINE (2000-2006), EMBASE (2000-2006) and the Cochrane Library (2006 Issue 3) using an appropriate search strategy. We will extend the search to other databases if necessary. Citations in key articles identified will be used to identify further relevant articles.

Searches will initially be conducted for publications from 2000. This will then be extended backwards as necessary and dependent on the volume of relevant literature.

Cross-sectional and cohort studies are the study design of choice for prevalence and incidence information. We will, therefore, initially select these types of studies.

Initially we will select UK based studies, extending this to Northern European studies or beyond as necessary.

The methodological quality of selected studies will be discussed.

Data on relevant outcomes will be extracted and tabulated.

Data analysis will be dependent on the availability of information.

7.3 Search strategies

7.3.1 ARIF Reviews Protocol (October 2006)

In the first instance the focus of ARIF's response to requests is to identify systematic reviews of research. The following will generally be searched, with the addition of any specialist sources as appropriate to the request.

1. Cochrane Library
- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database
An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments and Evidence Based guidelines
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes, Public Health excellence
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Co-ordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex STEER Reports
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases
- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts
- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products

7.3.2 Multiple Sclerosis Search Strategy

Database: Ovid MEDLINE(R) <1966 to October Week 1 2006>

1 exp multiple sclerosis/ (28332)
2 multiple sclerosis.mp. (33156)

3 or/1-2 (33272)
4 survey$.mp. (226823)
5 prevalence.mp. (221400)
6 incidence.mp. (367310)
7 cohort studies/ (71212)
8 or/4-7 (785737)
9 3 and 8 (2664)
10 limit 9 to ("reviews (optimized)" and yr="2000 - 2006") (223)
11 from 10 keep 1-223 (223)
12 exp multiple sclerosis/ (28332)
13 multiple sclerosis.mp. (33156)
14 or/1-2 (33272)
15 survey$.mp. (226823)
16 prevalence/ (96367)
17 incidence/ (106111)
18 cohort studies/ (71212)
19 or/15-18 (450655)
20 14 and 19 (1545)
21 limit 20 to ("reviews (optimized)" and yr="2000 - 2006") (114)
22 from 21 keep 1-114 (114)

Database: EMBASE <1980 to 2006 Week 44>

1 exp multiple sclerosis/ (26244)
2 multiple sclerosis.mp. (28524)
3 or/1-2 (28524)
4 survey$.mp. (547542)
5 prevalence/ (104694)
6 incidence/ (77719)
7 cohort analysis/ (37681)
8 or/4-7 (727562)
9 3 and 8 (2722)
10 limit 9 to ("reviews (2 or more terms min difference)" and yr="2000 - 2006") (264)
11 limit 10 to human (255)
12 from 11 keep 1-255 (255)

7.3.3 Motor Neurone Disease Search Strategy

Database: Ovid MEDLINE(R) <1966 to October Week 4 2006>

1 exp motor neuron disease/ (19169)
2 motor neuron disease.mp. (3655)
3 motor neurone disease.mp. (552)
4 (amyotrophic lateral sclerosis or als).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (29874)
5 lou gehrig$ disease.mp. (35)
6 progressive muscular dystrophy.mp. (998)
7 progressive bulbar palsy.mp. (60)
8 or/1-7 (42902)
9 survey$.mp. (227886)
10 Health Surveys/ (22919)
11 (incidence or prevalence).mp. (559640)
12 cohort studies/ (71695)
13 (cohort study or cohort studies).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (84251)
14 or/9-13 (797937)
15 8 and 14 (2474)
16 limit 15 to ("reviews (optimized)" and yr="2000 - 2006") (135)
17 limit 16 to humans (131)
18 from 17 keep 1-131 (131)

Database: EMBASE <1980 to 2006 Week 44>

1 exp motor neuron disease/ (10057)
2 motor neuron disease.mp. (3899)
3 motor neurone disease.mp. (372)
4 (amyotrophic lateral sclerosis or als).mp. (22358)
5 lou gehrig$ disease.mp. (34)
6 progressive muscular dystrophy.mp. (400)
7 progressive bulbar palsy.mp. (54)
8 or/1-7 (25327)
9 survey$.mp. (547542)
10 health survey/ (43362)
11 (incidence or prevalence).mp. (458553)
12 cohort studies/ (37681)
13 cohort$.mp. (93241)
14 or/9-13 (1023412)
15 8 and 14 (3147)
16 limit 15 to ("reviews (2 or more terms min difference)" and yr="2000 - 2006") (188)
17 limit 16 to human (182)
18 from 17 keep 1-182 (182)

7.3.4 Huntington's Disease Search Strategy

Database: Ovid MEDLINE(R) <1966 to November Week 1 2006>

1 Huntington Disease/ (6467)
2 huntington$ disease.mp. (7826)
3 huntington$ chorea.mp. (1111)
4 survey$.mp. (230293)
5 health surveys/ (23193)
6 (incidence or prevalence).mp. (565140)
7 (cohort or cohorts).mp. (131527)
8 cohort studies/ (72507)
9 or/1-3 (8018)
10 or/4-8 (839326)
11 9 and 10 (344)
12 limit 11 to (humans and "reviews (sensitivity)" and yr="2000 - 2006") (71)
13 from 12 keep 1-71 (71)

Database: EMBASE <1980 to 2006 Week 44>

1 huntington$ disease.mp. (4957)
2 huntington$ chorea.mp. (6961)
3 survey$.mp. (547542)
4 health surveys/ (43362)
5 (incidence or prevalence).mp. (458553)
6 (cohort or cohorts).mp. (93065)
7 cohort studies/ (37681)
8 or/3-7 (1023284)
9 or/1-2 (7534)
10 8 and 9 (699)
11 limit 10 to (human and "reviews (2 or more terms high sensitivity)" and yr="2000 - 2006") (83)
12 from 11 keep 1-83 (83)

Database: Ovid MEDLINE(R) <1966 to November Week 1 2006> (Primary studies)

1 huntington disease/ (6467)
2 huntington$ disease.mp. (7826)
3 huntington$ chorea.mp. (1111)
4 (incidence or prevalence).mp. (565140)
5 (cohort or cohorts).mp. (131527)

6 cohort studies/ (72507)
7 or/1-3 (8018)
8 or/4-6 (661337)
9 7 and 8 (265)
10 limit 9 to (humans and yr="2000 - 2006") (89)
11 from 10 keep 1-89 (89)

Database: EMBASE <1980 to 2006 Week 45> (Primary studies)

1 huntington$ disease.mp. (4970)
2 huntingtons chorea.mp. (499)
3 (incidence or prevalence).mp. (459337)
4 (cohort or cohorts).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (93288)
5 cohort studies/ (37824)
6 or/1-2 (5415)
7 or/3-5 (528653)
8 6 and 7 (193)
9 from 8 keep 1-193 (193)

7.3.5 Muscular Dystrophy Search Strategy

Database: Ovid MEDLINE(R) <1966 to November Week 1 2006>

1 muscular dystrophy.mp. (13224)
2 exp muscular dystrophies/ (16081)
3 (duchenne MD or duchenne muscular dystrophy).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4351)
4 (becker muscular dystrophy or becker MD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (873)
5 (dystrophia myotonica or myotonic dystrophy).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3987)
6 or/1-5 (20432)
7 survey$.mp. (230293)
8 Health Surveys/ (23193)
9 (incidence or prevalence).mp. (565140)
10 cohort studies/ (72507)
11 (cohort or cohorts).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (131527)
12 or/7-11 (839326)
13 6 and 12 (801)
14 limit 13 to ("reviews (sensitivity)" and yr="2000 - 2006") (153)
15 from 14 keep 1-153 (153)

Database: EMBASE <1980 to 2006 Week 44>

1 exp muscular dystrophy/ (13612)
2 muscular dystrophy.mp. (12099)
3 exp muscular dystrophy/ (13612)
4 (duchenne MD or duchenne muscular dystrophy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (5652)
5 (becker muscular dystrophy or becker MD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1355)
6 (dystrophia myotonica or myotonic dystrophy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3113)
7 survey$.mp. (547542)
8 Health Surveys/ (43362)
9 (incidence or prevalence).mp. (458553)
10 cohort studies/ (37681)
11 (cohort or cohorts).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (93065)

12 or/7-11 (1023284)
13 or/1-6 (14650)
14 12 and 13 (1095)
15 limit 14 to (human and "reviews (2 or more terms high sensitivity)" and yr="2000 - 2006") (117)
16 from 15 keep 1-117 (117)

Database: Ovid MEDLINE(R) <1966 to November Week 1 2006> (Primary studies)

1 muscular dystrophy.mp. (13224)
2 exp muscular dystrophies/ (16081)
3 (duchenne MD or duchenne muscular dystrophy).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4351)
4 (becker muscular dystrophy or becker MD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (873)
5 (dystrophia myotonica or myotonic dystrophy).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3987)
6 or/1-5 (20432)
7 (incidence or prevalence).mp. (565140)
8 cohort studies/ (72507)
9 (cohort or cohorts).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (131527)
10 or/7-9 (661337)
11 6 and 10 (681)
12 limit 11 to (humans and yr="2000 - 2006") (190)
13 from 12 keep 1-190 (190)

Database: Ovid MEDLINE(R) <1966 to November Week 2 2006> (Primary studies)

1 muscular dystrophy.mp. (13235)
2 exp muscular dystrophies/ (16095)
3 (duchenne MD or duchenne muscular dystrophy).mp. (4356)
4 (becker muscular dystrophy or becker MD).mp. (873)
5 (dystrophia myotonica or myotonic dystrophy).mp. (3992)
6 or/1-5 (20449)
7 (incidence or prevalence).mp. (566070)
8 cohort studies/ (72703)
9 (cohort or cohorts).mp. (131893)
10 or/7-9 (662549)
11 6 and 10 (681)
12 limit 11 to (humans and yr="1980 - 2000") (400)
13 from 12 keep 1-400 (400)

Database: EMBASE <1980 to 2006 Week 45> (Primary studies)
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1 muscular dystrophy.mp. (12106)
2 exp muscular dystrophy/ (13618)
3 (duchenne MD or duchenne muscular dystrophy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (5654)
4 (becker muscular dystrophy or becker MD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1356)
5 (dystrophia myotonica or myotonic dystrophy).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3114)
6 (incidence or prevalence).mp. (459337)
7 cohort studies/ (37824)
8 (cohort or cohorts).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (93288)
9 or/1-5 (14657)
10 or/6-8 (528653)
11 9 and 10 (590)
12 limit 11 to (human and yr="2000 - 2006") (229)
13 from 12 keep 1-229 (229)