families dependent on state benefits, one of the fastest growing and most disadvantaged groups in society. By any stretch of the imagination, economically inactive lone parents as a group are at least as disadvantaged as those in social classes IV and V, who are commonly contrasted with their more privileged counterparts in classes I and II. There is a strong case, therefore, for comparing the combined mortality records of social classes II, IV and V plus the unemployed to give the best aggregate picture of inequalities in child mortality.

If our analysis is valid, one consequence is that a greater proportion of observed health differences in childhood would be associated with socioeconomic variations in circumstances than can be accounted for by conventional social class groupings. Furthermore, an implicit corollary is that strategies to promote health should pay greater attention to financial hardship and other correlates of poverty than present policy seems inclined to do.

We must, however, acknowledge that the inferences on which the analysis in this paper are based are, of necessity, speculative. We believe that the assumptions we have made are reasonable and that the picture we paint is a valid one. Nevertheless, we have to concede that the evidence as it stands cannot be conclusive. Given that the implications are so profound, however, there is an urgent need to consider ways in which data from the 1991 census and vital registration can be linked in more illuminating ways so as to examine the phenomenon of the unoccupied in more depth.

We are grateful for comments and advice from the health statistics division of the Office of Population Censuses and Surveys.

4 (Department of Social Security, Research Report No. 6.)

(Accepted 25 January 1993)

Epidemiology of Alzheimer’s presenile dementia in Scotland, 1974-88

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Abstract

Objective—To describe the epidemiology of presenile Alzheimer’s disease in Scotland from 1974 to 1988.

Design—Retrospective review of hospital records of patients aged less than 73 years admitted to psychiatric hospital with various diagnoses of dementia. Diagnoses were classified by National Institute for Communicative Disorders and Stroke and Alzheimer’s Disease and Related Disorders Association Criteria and the Hachinski score. Completeness of the study sample was evaluated by scrutiny of neurology outpatient and general hospital records.

Setting—All general psychiatric hospitals in Scotland.

Subjects—All patients with onset of dementia aged 40-64.

Main outcome measures—Probable and broad Alzheimer’s disease, sex of patient, age at onset.

Results—5874 psychiatric hospital records, 129 neurology outpatient records, and 89 records from non-psychiatric hospitals were examined. 317 patients met criteria for probable Alzheimer’s disease, 569 met criteria for broad Alzheimer’s disease, and 267 met those for multi-infarct dementia. Minimal incidences per 100000 population aged 40-64 years were 22.6 (95% confidence interval, 20.2 to 25.2) and 40.5 (38.9 to 42.3) per 100000 for probable and broad Alzheimer’s disease. In the 1981 census year the annual incidence of probable Alzheimer’s disease was 1·6 (1.0 to 2.6). Women were at greater risk with incidence rates for probable Alzheimer’s disease of 28.2 (24.5 to 32.4) per 100000 compared with 16.5 (13.8 to 19.8) per 100000 for men. The incidence per 100000 for multi-infarct dementia was greater in men (25.1, 23.3 to 27.1) than women (13.4, 12.1 to 14.8).

Conclusion—Female sex seems to be positively associated with development of Alzheimer’s disease before age 65 years.

Introduction

Old people have the highest incidence of dementia, a condition with over 100 distinct causes.1 Although Alzheimer’s disease is the most important cause of dementia,2 there are few epidemiological data on the illness. Most studies have investigated senile dementia in relatively small populations.3 4 Although fewer people develop presenile Alzheimer’s disease,2 3 such patients are more likely to be known to the health service than older sufferers.4 Studies that use health service data to estimate the incidence and evaluate the natural course of presenile Alzheimer’s disease may be considerably more accurate and informative than those of senile disease.5 Substantial progress has been reported in understanding the molecular pathology of presenile Alzheimer’s disease6 but this cannot be extrapolated to senile forms before the epidemiology of presenile disease is known.

Incidence of disease needs to be known for aetiological studies but is also important to those planning diagnostic services within the health service. For

Alzheimer’s disease

Subjects and methods

We obtained data by retrospective examination of hospital records. In Scotland all patients receive a hospital diagnostic code from the International Classification of Diseases (ICD ninth revision) on admission, discharge, or death, and this information is available from the information and statistics division of the Scottish Home and Health Department.

The distinction between senile and presenile dementia is set at age 65 years, but some patients with senile onset may not be admitted until after 65. Our preliminary studies estimated that an upper age limit of 73 years at admission would identify over 97% of those patients with onset before 65 years.

We obtained data from the information and statistics division on all patients aged less than 73 years with a diagnostic code of Alzheimer’s disease, senile dementia, presenile dementia, arteriosclerotic dementia, senile dementia with acute confusional state, or dementia unspecified attending all general psychiatric hospitals during 1974 to 1988. Two experienced observers (GM and CM) examined the hospital records. A third observer (LJW) blindly examined a randomly chosen sample of 100 records of patients with presenile dementia, and interobserver reliability in the diagnosis of Alzheimer’s disease was tested by Cohen’s $\kappa$ statistic.11 Patients were included who had presented aged 40 to 64 years with documented features of dementia. The lower age limit was set by the National Institute for Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRA)12 and the upper age set by convention for presenile dementia. These criteria and a Hachinski score13 were applied to each record as described previously.14 Patients were classified into three groups: (a) ‘probable’ Alzheimer’s disease if they met the clinical criteria and had a Hachinski score less than 515; (b) ‘broad’ Alzheimer’s disease defined after reclassification of all presenile patients by discriminant analysis16 (this group included all probable Alzheimer’s disease); and (c) multi-infarct dementia—a definite history of at least one cerebrovascular accident and a Hachinski score greater than 6.17

Denominators for incidence were taken from the 1981 census and used to estimate the ‘at risk’ population aged 40 to 64 years. We calculated 95% confidence intervals with exact error factors for Poisson mean for numbers less than 30 and with the asymptotic error factor approximation $e^{-n}$ for larger numbers. Mantel-Haenszel weights were used for summary risk ratio estimation.

The assumption that all patients with presenile Alzheimer’s disease are known to psychiatric services was tested by reference to further data sources. In Scotland death certificates record primary, secondary, and tertiary causes of death, and institution of death. This information was requested from the registrar general wherever presenile dementia or Alzheimer’s disease was a cause of death before the age of 73. Hospital records were sought for such patients who had died in care outside psychiatric hospitals. Two neurology departments where registries of outpatients are maintained (Western General Hospital, Edinburgh, and Ninewells Hospital, Dundee, together serving about 20-25% of the Scottish population) allowed scrutiny of records of patients aged less than 73 years with a diagnosis of dementia. Advice was sought from all chief administrative medical officers about the care of patients with presenile dementia. Views were also obtained from local family doctor committees and from medical advisers to the Mental Welfare Commission. These sources confirmed that most patients were cared for within psychiatric services. In Grampian all psychiatric patient contacts since 1963 are notified to the Grampian psychiatric case register, search of the register found no outpatient with presenile Alzheimer’s disease who had never been admitted to psychiatric hospital.

Ethical approval to scrutinise hospital records was obtained from ethics committees of all health boards in Scotland and from the privacy committee of the Scottish Home and Health Department.

Results

The Information and Statistics Division identified 6581 patients. We located 5874 hospital records, 1217 of which were for demented patients aged 40 to 64 years at presentation; 707 records were either lost or contained insufficient information to apply the diagnostic criteria. Scrutiny of 1217 case records identified 569 broad cases of Alzheimer’s disease (of which 317 were probable cases) and 267 cases of multi-infarct dementia. We assumed that at each hospital the same proportion of missing or inadequate records (317/5167=6.1%) were cases of Alzheimer’s disease and estimated that about 43 cases of probable Alzheimer’s disease (6-1% of 707) were omitted because of lost or inadequate records.

Tables I and II give the age sex-specific incidences and female to male ratios for probable and broad Alzheimer’s disease. Increasing age and female sex were associated with an increased incidence of Alzheimer’s disease. The summary sex risk ratios for probable and broad Alzheimer’s disease were similar. Crude division of overall incidence by 15 (number of years of studied) gave annual rates of 1.5 per 100 000 and 2.7 per 100 000 for probable and broad Alzheimer’s disease respectively. These compare with the actual rates of 1.6 (95% confidence interval 1.0 to 2.6) and 3.5 per 100 000.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Men</th>
<th>Women</th>
<th>All</th>
<th>Female to male ratio</th>
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<tr>
<td>40-44</td>
<td>0.7</td>
<td>2.0</td>
<td>1.4</td>
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<tr>
<td>45-49</td>
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<tr>
<td>50-54</td>
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<td>55-59</td>
<td>29.6 (21.8 to 40.3)</td>
<td>48.9 (39.0 to 61.4)</td>
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<td>1.7</td>
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<tr>
<td>60-64</td>
<td>27.1 (19.1 to 38.5)</td>
<td>40.8 (36.5 to 59.9)</td>
<td>37.8</td>
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<tr>
<td>Total</td>
<td>165 (13.8 to 19.8)</td>
<td>262 (24.5 to 32.4)</td>
<td>226 (20.2 to 25.2)</td>
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*Mantel-Haenszel summary estimate.

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<tr>
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<td>10.1 (5.5 to 16.9)</td>
<td>13.7 (8.4 to 21.1)</td>
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<tr>
<td>50-54</td>
<td>29.4 (21.7 to 39.9)</td>
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<tr>
<td>55-59</td>
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<tr>
<td>60-65</td>
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<td>99.5 (87.8 to 104.5)</td>
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<td>Total</td>
<td>28.1 (26.1 to 30.2)</td>
<td>52.0 (49.4 to 54.7)</td>
<td>40.5 (38.9 to 42.3)</td>
<td>1.8*</td>
</tr>
</tbody>
</table>

*Mantel-Haenszel summary estimate.


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<tr>
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<td>13.4</td>
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(2.6 to 4.7) per 100,000 for probable and broad Alzheimer’s disease for the 1981 census year. Women had significantly less risk of multi-infarct dementia than men (table III).

**Validity**

We sought 169 records from district general or teaching hospitals and 34 from cottage or private hospitals. The hospital records of 199 patients with presenile dementia who died in institutions other than psychiatric hospitals were requested but only 89 were located because over half of these records were destroyed after death. All 89 met study criteria for presenile dementia; nine of these records were of patients with probable Alzheimer’s disease, but only three had not been admitted to a psychiatric hospital. This suggests that among the 199 records at least seven were of Alzheimer patients.

Review of neurology department registries found 129 outpatient records; 24 met the criteria for probable Alzheimer’s disease and 20 of these noted admission(s) to psychiatric hospital. The remaining four records were of patients who had presented to neurology departments after 1983. These figures suggest that about 20 Alzheimer patients remained solely as neurology outpatients throughout Scotland during 1974-88.

Kappa values of 0.72 and 0.61 were obtained for comparisons between the two observers (GM and CM) and the blinded observer (LJW). This represents substantial agreement between the two main observers and the third in the diagnosis of probable Alzheimer’s disease.16

**Discussion**

Our rates of broad and probable Alzheimer’s presenile dementia are minimum estimates of the true incidence. Previously we estimated that our data request omitted 6-5% of cases2 and we now add a further 6-1% who may have been lost because of inadequate records. These omission errors are small compared with the effects of changes in diagnostic criteria: rates in our broad class are more than double those in the probable class. Although our method of classification is novel and requires further validation,4 the main findings were unaffected by choice of diagnostic criteria. Female sex was significantly associated with the risk of Alzheimer’s disease no matter how dementia was classified. Small numbers of patients aged less than 55 make interpretation of a sex effect in this group inappropriate. Different ascertainment methods have consistently found female sex to be a risk factor in surveys of senile Alzheimer’s disease,2,10 but a significant association between female sex and presenile Alzheimer’s disease has not been reported. Significantly more men than women had multi-infarct dementia diagnosed.20

Patients identified as having multi-infarct dementia represent a distinct clinical subgroup within the study sample, but it is debatable whether they accurately represent all patients with this disease in the population. The point of health service contact for patients with cerebrovascular disease and dementia is variable and dependent on several factors that we did not evaluate—for example, location and progression of cerebral disease, relative dominance of symptoms, etc. Variation in use of health care between the sexes does not explain the strong association between Alzheimer’s disease and female sex.

**Care of Patients**

We tested the assumption that most patients with presenile Alzheimer’s disease are eventually admitted to psychiatric hospital. If alternative pathways of health care provision were used extensively we would have had serious underascertainment. Alzheimer patients may never present to medical attention but die in the community either undiagnosed or cared for by relatives who have never sought medical investigation. The insidious course, the behavioural disturbances, and the distress of Alzheimer’s disease make this uncommon. General practitioners can determine the pattern of later health care delivery in Alzheimer’s disease and may not refer to specialist outpatient care. Local family doctor committees throughout Scotland advised that most, if not all, such patients were referred to specialists. Our study was retrospective and because the quality of general practitioners’ records varies and most records are destroyed after a patient dies, it was not possible to include such patients in our study. The total number of Alzheimer patients who followed this pathway remains unknown, but community care is much rarer in Scotland than in England and Wales.

Patients with Alzheimer’s disease could be referred for specialist investigation but never admitted. Only 3% (4/129) of patients with dementia who attended two neurology outpatient departments were not admitted to psychiatric hospital. These observations were consistent with advice received from experienced physicians in Scotland and indicate that this is a small source of error (about 20 Alzheimer patients for all Scotland). It is also possible for patients to be admitted directly to general hospitals and never to psychiatric hospital. Of the 89 records we scrutinised, only three were of patients with probable Alzheimer’s disease who had never been admitted to psychiatric hospital.

The reported incidences of Alzheimer’s disease (derived from records of patients admitted to hospital) were consistent with results reported by other investigators who used different case ascertainment methods. An annual incidence rate of 2.4/100 000 at risk population was reported for presenile probable Alzheimer’s disease in another national study.1 In summary, evidence from several independent data sources indicate that our ascertainment method was not systematically biased in respect of the study’s main findings. Our results suggest that female sex is a risk factor in presenile Alzheimer’s disease. The pressing question is what is it about being female that increases the risk of this condition?

This study was supported by the Medical Research Council (Grant No. G9096112N). We thank Dr Cole and staff of Information and Statistics Division, the registrar general for Scotland, and all medical records staff who helped in the study.

Selective serotonin reuptake inhibitors: meta-analysis of efficacy and acceptability

Fujian Song, Nick Freemantle, Trevor A Sheldon, Allan House, Paul Watson, Andrew Long, James Mason

Abstract

Objective—To examine the evidence for using selective serotonin reuptake inhibitors instead of tricyclic antidepressants in the first line treatment of depression.

Design—Meta-analysis of 63 randomised controlled trials comparing the efficacy and acceptability of selective serotonin reuptake inhibitors with those of tricyclic and related antidepressants.

Main outcome measures—Improvement in mean scores on Hamilton depression rating scale for 53 randomised controlled trials. Pooled drop out rates from the 58 trials which reported drop out by treatment group.

Results—Among the 20 studies reporting standard deviation for the Hamilton score no difference was found in efficacy between serotonin reuptake inhibitors and tricyclic and related antidepressants (standardised mean difference 0.004, 95% confidence interval −0.096 to 0.105). The difference remained insignificant when the remaining 33 studies that used the 17 item and 21 item Hamilton score were included by ascribing weighted standard deviations. The odds ratio for drop out rate in patients receiving serotonin reuptake inhibitors compared with those receiving tricyclic antidepressants was 0.95 (0.86 to 1.07). Similar proportions in both groups cited lack of efficacy as the reason for dropping out but slightly more patients in the tricyclic group cited side effects (18.8% v 15.4% in serotonin reuptake group).

Conclusions—Routine use of selective serotonin reuptake inhibitors as the first line treatment of depressive illness may greatly increase cost with only questionable benefit.

Introduction

Selective serotonin reuptake inhibitors are a relatively new class of antidepressants that have been heavily promoted for use as first line treatment in depression. They are the most commonly prescribed antidepressant in the United States, but their routine use in Britain is controversial. The high specificity of serotonin reuptake inhibitors, without antagonism of neurotransmitter receptors or direct cardiac effects, has led to the expectation that they have the same antidepressant activity as tricyclic and related antidepressants but do not produce many of the common side effects. Thus it is claimed that they have two important advantages over tricyclic and related antidepressants—they are better tolerated and are less toxic in overdose. However, disagreement exists about the role of serotonin reuptake inhibitors in treating major depression.

One reason for these differences of opinion is that the claims made for serotonin reuptake inhibitors are often based on the results of individual trials. Many of the studies are not large enough to detect or exclude with certainty clinically relevant differences in the effects of serotonin reuptake inhibitors and tricyclic and related drugs. We reviewed the evidence for the efficacy and acceptability of serotonin reuptake inhibitors compared with the tricyclic and related antidepressants by meta-analysis. We included data from all comparable randomised controlled trials, which enables smaller effects to be detected or excluded with confidence. The large number of studies also gives the findings potentially greater generalisability.

Methods

We conducted a meta-analysis of the results of efficacy studies and of the drop out rates. We identified 64 randomised controlled trials comparing serotonin reuptake inhibitors with tricyclic or related antidepressants by searching Medline and Index Medicus, manual cross referencing, and discussion with experts (table I). One study did use a double-blind design and was therefore excluded from the analysis. Some multicentre studies have been published in aggregate and separately, and we took great care to avoid including the same results more than once.

EFFICACY

The trials used various psychometric instruments to measure the efficacy of treatments. The most consistently used instrument, the Hamilton depression rating scale, was included in 61 of the trials. The Hamilton depression rating scale is a reliable instrument that is particularly weighted towards and sensitive to change in somatic symptoms rather than psychological and cognitive factors. Most studies used either the 17 question or the 21 question instrument, although other versions were occasionally used. However, it is generally accepted that none of the items which supplement