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Exposure to antidepressants and the risk of cryptogenic fibrosing alveolitis: a case-control study

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Exposure to antidepressants and the risk of cryptogenic fibrosing alveolitis: a case-control study. R. Hubbard, A. Venn, J. Britton. ©ERS Journals Ltd 2000.

ABSTRACT: The explanations for the emergence of cryptogenic fibrosing alveolitis as a new clinical entity during the second half of the 20th century are unclear. The authors have previously reported evidence of an increased risk of cryptogenic fibrosing alveolitis in relation to the use of antidepressant drugs.

The authors have now tested this hypothesis a priori in an analysis of computerized general practice records for 890 cases of cryptogenic fibrosing alveolitis and 5,884 matched controls drawn from the UK General Practice Research Database.

Exposure to antidepressants at the time of diagnosis was increased in cases compared to controls (odds ratio (OR) 1.52, 95% confidence interval (95% CI) 1.24–1.86), and this increase remained if the analysis was restricted to exposures 4 yrs prior to diagnosis (OR 1.50, 95% CI 0.98–2.30). However this increased prescribing was not specific to any particular class of antidepressant or individual drug, and there was no evidence of a dose-response relationship between exposure to amitriptyline (the most commonly prescribed antidepressant) and disease.

The presented data do not allow any firm conclusion to be made as to whether there is a causal relationship between antidepressant exposure and cryptogenic fibrosing alveolitis, but it seems unlikely that exposure to tricyclic antidepressants shortly before diagnosis is a strong risk factor for cryptogenic fibrosing alveolitis.
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Cryptogenic fibrosing alveolitis (CFA) is the most common of the interstitial lung diseases [1], but it is a new clinical entity which has emerged as a significant cause of morbidity and mortality only during the second half of the 20th century [2, 3]. The aetiology of CFA remains unclear, but occupational exposure to dust [4–6] and cigarette smoking [5, 7] have been identified as potential risk factors for the disease.

Pulmonary fibrosis is a well recognized complication of a number of drugs including amiodarone and bleomycin [8], but has also been reported anecdotally as an adverse reaction to a number of more commonly used drugs including the antidepressants dothiepin [9, 10] and desipramine [11]. It is therefore possible that rare unrecognized adverse reactions to some commonly prescribed drugs may contribute to the aetiology of CFA. The authors have previously reported a case-control study of exposure to five groups of commonly prescribed drugs (antidepressants, β-blockers, anticonvulsants, antibiotics and non-steroidal anti-inflammatory drugs) in patients with CFA and age, sex and community matched controls. No evidence of an increase in disease risk was found in relation to four of these drug groups, but the authors did find evidence of an increased risk of CFA following the use of antidepressants [12]. This effect extended to exposures which predated disease diagnosis by ≥5 yrs. The strongest effects were associated with imipramine (a precursor of desipramine, odds ratio (OR) 4.90, 95% confidence interval (95% CI) 1.28–18.71) and dothiepin (OR 4.64, 95% CI 0.91–23.58). More recently it has been demonstrated that the lung is a reservoir for antidepressants and that 75% of an injected dose of imipramine remains bound within the lung [13], suggesting that pulmonary exposure to antidepressants is likely to be disproportionately high. However, no mechanism for how imipramine may cause CFA has been proposed.

Since exposure to specific antidepressants is potentially avoidable the authors have followed-up the findings of their initial study to test *a priori* the hypothesis that exposure to antidepressants, and in particular imipramine and dothiepin, is associated with CFA in a case-control study using the UK General Practice Research Database (GPRD).

Methods

The subjects consisted of 890 cases of CFA and 5,884 age, sex, and community matched controls drawn from the GPRD. The GPRD is the largest primary care population database in the UK [14], comprising longitudinal data from over 7 million patients. Data collection for the GPRD started in 1987, although the majority of practices were recruited in the 1990s and the average number of years of data for each participant is six. The cases and controls have previously been described in detail in an analysis of lung cancer incidence in patients with CFA

For editorial comments see page 381.

[15]. Briefly, cases were defined as those with a diagnosis of CFA recorded anywhere in the GPRD record, and the date of diagnosis defined as the date of this condition. The authors have previously reviewed hospital clinic letters for a subsample of these cases and established that the diagnosis of CFA in the GPRD is reliable [15]. Six controls were individually matched to each case as the six individuals of the same sex, registered at the same general practice and closest in age to the case. For the purpose of extracting prescribing data, controls were assigned a "pseudo date of diagnosis" to match their case. Since CFA is known to occur in association with connective tissue diseases, and such patients may have increased exposure to antidepressants due to symptoms of chronic pain, all cases and controls with a recorded diagnosis of connec-tive tissue were excluded from the analysis.

Data on all antidepressant prescriptions prior to date of diagnosis were extracted for cases and controls. Antidepressant exposure was then recoded into three levels as follows: exposure to any antidepressant, exposure to one of the three main groups of antidepressants (tricyclic and related antidepressants, monoamine oxidase inhibitors (MAOIs) or selective serotonin (5-hydroxytryptamine) reuptake inhibitors (SSRIs)), exposure to individual antidepressants. In order to study the probable timing and magnitude of increased prescribing due to reverse causation, prescription data for the diuretic furosemide were also identified. Data on smoking were available from the previous study coded as current cigarette smoker, current pipe/cigar smoker, exsmoker or nonsmoker [15]. An initial descriptive analysis was performed to summarize the demographic details of subjects and calculate the number of years of available longitudinal data. The association between antidepressant exposure up to the time of diagnosis of CFA was estimated using conditional logistic regression. The analysis was completed first for exposure to any antidepressant, then to specific classes of antidepressant and finally to individual drugs, although the primary hypothesis was that there would be an association between cryptogenic fibrosing alveolitis and exposure to tricyclic antidepressants, and in particular dothiepin or imipramine. Due to the limitations of statistical power analysis for individual drugs analyses were only undertaken where the exposure rate was >1% in either the cases or controls. Where evidence of a significant effect due to an individual drug was found a dose-response analysis was performed estimating the total drug exposure rate from the number of days prescribed, the daily dose and the duration of prescribing data. Evidence of confounding by smoking habit was sought by adding the smoking variable to the model. Interaction terms were introduced, as appropriate, to test for effect modification by age, sex and smoking habit. To explore for possible reverse causation these analyses were repeated for exposures predating the date of diagnosis by 1, 2, 3, and 4 yrs and the effect on the OR observed. For comparative purposes a similar analysis was performed by extracting and analysing data for the diuretic furosemide, since it seems likely that the use of this drug will increase in response to the signs and symptoms of CFA. All analyses were conducted using Stata version 5 (Stata Corporation, College Station, TX, USA). In the previous study the OR for antidepressant exposure was 1.79 and 21% of controls were exposed. In the present study only recent prescribing data were available, and so the control antidepressant exposure rate was estimated at 10%. With a ratio of six controls to each case a total of 600 cases would provide in excess of 90% power to detect an OR of $\geq$1.6 (power calculation in EGRET SIZ Cytel Software Corporation, Seattle, WA, USA for matched case-control studies [16]).

Results

The median age of the cases was 71 yrs (interquartile range 64–78 yrs) and 553 (62%) were male; since controls were matched by age and sex results were identical for controls [15]. The median duration (interquartile range) of available validated prescribing data prior to date of diagnosis was 3.5 yrs (2.1–5.0 yrs). For controls with available smoking data (n=3,752, 64%) 909 (24%) were current cigarette smokers, 107 (3%) were current pipe/cigar smokers, 327 (9%) were exsmokers and 2,409 (64%) were nonsmokers [15]. For cases with available smoking data (n=624, 70%) 169 (27%) were current cigarette smokers, 9 (1%) were current pipe/cigar smokers, 64 (10%) were exsmokers and 382 (61%) were nonsmokers [15].

The numbers and percentages of cases and controls ever exposed to any antidepressant, a tricyclic or related antidepressant, an SSRI antidepressant or an MAOI antidepressant are shown in table 1. Except for MAOIs, where exposure levels were very low, more cases than controls had been exposed to all the major categories of antidepressants. There was no evidence of confounding by smoking habit and no evidence of effect modification by age, sex or smoking habit. For individual antidepressants exposure levels were generally low (table 2). Antidepressants with a $\geq$1% exposure in either the cases or controls included; amitriptyline, dothiepin, lofepramine, paroxetine and fluoxetine. For each of these antidepressants more cases than controls had been exposed, but the size of these effects were small, and for all except amitriptyline the 95% CIs included unity (table 2). There was no evidence of a dose response relationship between exposure

Table 1. – Association between main categories of antidepressant use, furosemide and cryptogenic fibrosing alveolitis

Drug group	Cases (n=890)	Controls (n=5884)	Odds ratio	95% CI	*p-value
Any antidepressant	146 (16.4)	686 (11.7)	1.52	1.24–1.86	0.0001
Tricyclic and related antidepressants	126 (14.2)	619 (10.5)	1.44	1.16–1.78	0.0011
SSRIs	35 (3.9)	126 (2.1)	1.85	1.25–2.74	0.0035
MAOIs	1 (0.1)	4 (0.7)			
Furosemide	213 (23.9)	442 (7.5)	4.39	3.60–5.36	0.0001

Data are absolute values with percentages in parentheses. 95% CI: 95% confidence interval; SSRIs: selective serotonin reuptake inhibitors; MAOIs: monoamine oxidase inhibitors. *: likelihood ratio test.

Table 2. – Effect of individual antidepressants on risk of cryptogenic fibrosing alveolitis

Drug group	Cases (n=890)	Controls (n=5884)	Odds ratio*	95% CI	p-value**
Tricyclic and related					
Amitriptyline	47 (5.3)	197 (3.4)	1.62	1.16–2.27	0.007
Amoxepine	0	2 (0.03)			
Clomipramine	8 (0.9)	30 (0.5)			
Desipramine	1 (0.1)	1 (0.02)			
Dothiepin	50 (5.6)	282 (4.8)	1.22	0.89–1.67	0.2
Doxepin	3 (0.3)	25 (0.4)			
Imipramine	4 (0.5)	43 (0.73)			
Lofepramine	24 (2.7)	116 (2.0)	1.39	0.88–2.19	0.2
Maprotiline	0	2 (0.03)			
Mianserin	3 (0.3)	25 (0.4)			
Nortriptyline	4 (0.5)	21 (0.4)			
Protriptyline	1 (0.1)	3 (0.05)			
Trazodone	7 (0.8)	27 (0.5)			
Trimipramine	8 (0.9)	32 (0.5)			
SSRIs					
Citalopram	0	0			
Fluoxetine	16 (1.8)	74 (0.1)	1.39	0.80–2.41	0.3
Fluvoxamine	4 (0.5)	7 (0.1)			
Paroxetine	12 (1.4)	42 (0.7)	1.86	0.95–3.62	0.083
Nefazodone	1 (0.1)	0			
Sertraline	7 (0.8)	21 (0.36)			
Venafaxine	0	0			
MAOIs					
Isocarboxazid	1 (0.1)	0			
Moclobemide	0	1 (0.02)			
Phenelzine	0	1 (0.02)			
Tranylcypromine	0	2 (0.03)			
Others					
Flupenthixol	8 (0.9)	54 (0.9)			
Tryptophan	0	1 (0.02)			

Data are absolute numbers with percentages in parentheses. *: calculated if exposure prevalence >1% in cases or controls; **: likelihood ratio test. 95% CI: 95% confidence interval; SSRIs: selective serotonin reuptake inibitors; MAOIs: monoamine oxidase inhibitors.

to amitriptyline and disease (OR per increase in gram of amitriptyline per year 1.00, 95% CI 0.99–1.01, p=0.9).

In the analysis of reverse causation the number of cases contributing data at 1, 2, 3 and 4 yrs prior to diagnosis was 889, 626, 465, 320 and 184 respectively whilst the number of controls was 5,870, 4,336, 3,254, 2,220 and 1,273. The results of the analysis for reverse causation are shown graphically in figures 1 and 2. The size of the increase in antidepressant exposure remained relatively constant over time even up to 4 yrs prior to diagnosis (OR 1.50, 95% CI 0.98–2.30). In contrast there was a marked increase in exposure to furosemide amongst cases at the time of diagnosis (OR 4.39, 95% CI 3.60–5.36), but this effect fell rapidly with increasing years prior to diagnosis, although even 4 yrs prior to the date of diagnosis cases were more than twice as likely to receive prescriptions for furosemide than controls (OR 2.39, 95% CI 1.05–5.41).

Discussion

The results of this study demonstrate that there is a small increase in the prescribing of antidepressants to patients with CFA compared to age, sex and general practice matched controls, and that this increase precedes diagnosis by at least 4 yrs. In contrast to the findings of a previous study [12] strong specific effects of individual drugs such as imipramine and dothiepin were not found.

The GPRD is the largest longitudinal primary care database in the UK and contains detailed information on prescribing and morbidity [14]. The size of the GPRD means that it is able to yield considerable numbers of cases for even uncommon conditions, and the case population detailed in this study is the largest reported to date. The use of the nested case-control design has the advantage of minimizing recall and selection bias, however there are disadvantages to using General Practice datasets. The first and most relevant to this study is that only an average of 3–4 yrs of longitudinal data are available, and this limits the ability to exclude reverse causation, that is that the increase in prescribing is actually secondary to symptoms of disease itself. In order to try to exclude reverse causation sufficient longitudinal data are required to show an association between disease and drug exposure before symptoms of disease are present. Previous clinical descriptions of CFA suggest that the average duration of symptoms prior to diagnosis is $\leq$2 yrs, but that a wide range of natural histories are present [12, 17]. Thus to try to minimize reverse causation the analysis needs to be undertaken at least 5 yrs prior to the date of diagnosis and at present there are insufficient years of data in the GPRD to do this. For this reason the authors adopted the additional

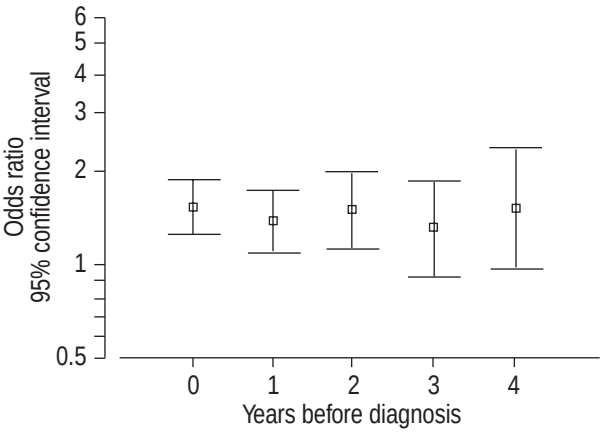

Fig. 1. – Antidepressant exposure.

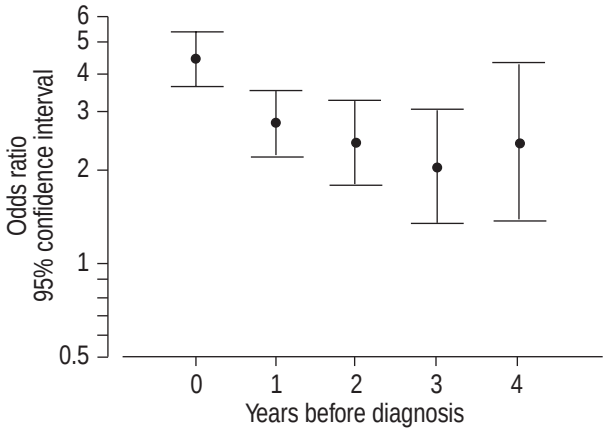

Fig. 2. – Furosemide exposure.

approach of examining the pattern of association seen with a drug likely to be strongly influenced by reverse causation, and chose the diuretic furosemide as CFA is commonly misdiagnosed as heart failure. An alternative approach would have been to use a control group who also had a chronic illness, but the authors chose not to do this because with such a design it is often more difficult to predict the size and even the direction of the bias. Another problem associated with the use of general practice databases is the accuracy of diagnoses, although in general the accuracy of diagnoses in the GPRD has been reported to be high [14, 18]. In a previous study the current authors reviewed the hospital correspondence for a subsample of 20 of the cases of CFA and confirmed the diagnosis in all but one case [15]. Furthermore, if misclassification of case-status is present within the dataset because some of the cases have been incorrectly diagnosed, then this will lead to an underestimate of any true effect of antidepressants.

In the present study the authors did find evidence of a small, generalized increase in antidepressant exposure in cases compared to controls, consistent with the findings of the pilot study [12]. However, there was virtually no prescribing of MAOIs, imipramine or mianserin, reflecting the fact that prescribing habits have changed, and so these candidate exposures could not be examined. No strong associations were found with specific antidepressants, such as dothiepin, and this, together with the lack of a dose-response relationship with amitriptyline (the most common exposure), argues against the relationship being causal.

Possible explanations for the small increase in antidepressant prescribing in cases include confounding and problems of bias, and in particular reverse causation. The authors controlled for age and sex by matching, but did not have data on other potential confounders such as occupation and socioeconomic status. Furthermore, although the authors adjusted for the effects of smoking in the analysis, it has previously been demonstrated that it is likely that a significant number of exsmokers are misclassified as nonsmokers in the GPRD [15] and thus there is potential for residual confounding. Although the size of the association with antidepressants was constant over the 4 yrs leading up to diagnosis, as detailed above, there are insufficient years of data to safely exclude reverse causation. As predicted there was a marked increase in furosemide exposure up to the date of diagnosis. Cases were twice as likely as controls to be prescribed diuretics even 4 yrs before diagnosis, suggesting that there were signs and/or symptoms of CFA at this time point.

In summary, the authors have found evidence that patients with cryptogenic fibrosing alveolitis have a small increase in exposure to antidepressants shortly before diagnosis. The findings of the present study suggest that this association is more likely to be due to bias resulting from reverse causation than a causal effect. However, the limited number of years of prescribing data mean that no firm conclusions can be made, but it seems unlikely that there is a strong effect of antidepressants shortly before diagnosis. To answer this question definitively an analysis of a dataset with sufficient longitudinal years to confidently exclude reverse causation is required.

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