Iatrogenic depression in the elderly
Results from a community-based study in the Netherlands

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Abstract Background The aim of this study was to investigate the association between the use of medication and depression in the elderly. Method A cross-sectional population-based study was conducted. Associations between the use of medication and depression are corrected for eight other etiological correlates of depression. The sample consisted of 2646 elderly people living in 11 municipalities in the Netherlands. Subjects were taken from the Longitudinal Aging Study Amsterdam, a 10-year longitudinal study on predictors and consequences of changes in well-being and autonomy in the older population. Associations are expressed in odds ratios (95% Confidence Intervals) between the use of (groups of) medication and depression. Results are adjusted for age, sex, urbanicity, socioeconomic status, physical health, social and interpersonal support, co-morbidity with other psychiatric disease and personality. The Population Attributable Risk percentage was calculated for selected groups of medication. Results After correction for competing risk factors of depression, 22 individual medications and nine groups of medications had unique associations with depression. Conclusions The use of depressogenic medication is an independent etiological factor in the pathogenesis of depression.

Key words depression – elderly – drugs – side-effects – etiological factors

Introduction

There is little qualitative doubt that depression can be caused, provoked or continued by drugs prescribed for other reasons. The quantitative significance of iatrogenesis as an etiological factor in depression is not that clear because research on this topic is scarce. Research should be carried out in a population with frequent use of medication and a high prevalence of depressive symptoms. These conditions can be met in the elderly.

In previous studies [1–3] the relationship was investigated between the use of depressogenic medication and different types of depression. In a population-based pilot-study [2], depressogenic medication was significantly more related to non-major depressive disorder (MDD) than to MDD. In a clinical sample of 195 elderly depressed persons [3], adjusted for the influence of a number of other etiological variables, the use of depressogenic medication was an independent etiological factor.

Depression, physical illness and physical disability exert mutually enforcing influences on each other [4]. A major objection against the methodology of previous studies was that no consideration was given to the confounding health and disability factors closely associated with the prescription of drugs. In a discussion in the British Medical Journal, initiated by an article on ‘Use of calcium channel blockers and risk of suicide’ [5, 6] the same type of objections did arise.

The present study, in a large Dutch elderly population sample, attempts to disentangle the etiological web of physical illness, depression and medication a step further. In a survey of the literature [7], several domains of variables were identified which have been shown to be associated with depression in the elderly. In the present study we have incorporated the following domains: age, sex, urbanicity, socioeconomic status, physical health,
social and interpersonal support, comorbidity with other psychiatric disease and personality. For all the medication used, we established the association of medication use with depression. The other etiological domains were considered as potential confounding factors and were hence controlled for.

### Subjects and methods

#### Sampling and response

The Longitudinal Aging Study Amsterdam (LASA) is a 10-year longitudinal study on predictors and consequences of changes in well-being and autonomy in the older population [8]. Sampling procedures and response were detailed earlier [7, 9], but will be briefly described here. Random samples of older (55–85) inhabitants were drawn from population registers in 11 municipalities in three regions of the Netherlands. The sample was stratified for age and sex. Persons aged 85 and above were excluded, because the attrition rate of this age group was expected to be too high over the 10-year study period. The sample was used in two studies: NESTOR-LSN [10] and LASA. For LASA, all 3805 respondents to the NESTOR-LSN interview (response rate 62.3%) were approached, of whom 3107 (81.7%) took part [9]. Three hundred and ninety-four persons (10.4%) refused to participate because of lack of interest; 134 (3.5%) were too ill or cognitively impaired to be interviewed; 126 (3.3%) died before being interviewed; and 44 persons (1.2%) could not be contacted. Attrition was related to age (p < 0.05) but not to sex. As expected the older old were more often found to be too ill or cognitively impaired to participate (p < 0.05). Due to item non-response on the instrument used to screen for depression, a further 51 subjects were lost. Finally, reliable data on medication use could not be obtained for 410 persons, leaving a study sample of 2646.

All interviews were conducted in the homes of respondents by specially trained and intensively supervised interviewers. All interviews were tape-recorded in order to control the quality of the data. Interviewers worked with laptop computers and were encouraged to record any disturbance in the course of the interviews. Interviews were conducted between October 1992 and October 1993.

Before inclusion in the study all participants gave their informed consent according to the prevailing legal requirement in the Netherlands. Moreover, the study was approved by the ethical committee of the Vrije Universiteit.

#### Measures

**Measuring depression**

For the purpose of this paper, depression was defined as all clinically relevant depressive symptoms not necessarily fulfilling rigorous diagnostic criteria for major depression as defined by DSM-III [11]. The prevalence of depression was measured using the Center for Epidemiologic Depression Scale (CES-D) [12]. This is a 20-item self-report scale developed to measure depressive symptoms in the community. It has been widely used in older community samples and has good psychometric properties in these samples [13, 14]. The Dutch translation had similar psychometric properties in three previously studied samples of elderly in the Netherlands [15]. The overlap with symptoms of physical illness has been shown to be minimal in a number of studies [17, 18]. The CES-D generates a total score which can range from 0 to 60. In order to identify respondents with levels of depression that are clinically relevant, we used the generally used cut-off score ≥16 [14, 15]. Criterion validity of the CES-D for major depressive disorder was excellent (sensitivity 100%, specificity 88%) [16].

**Medication use**

During the interview the interviewer asked the respondent to produce every bottle and box of prescription and non-prescription medication available in the house, and then evaluated, with the respondent, the actual use of medication. This actual use was registered on a form. A medical doctor checked this registration and computerisation took place using codes according to the Anatomical Therapeutical Chemical classification of the WHO. This classification enables individual and groupwise analysis of medication use.

#### Independent variables

As stated in the introduction, eight domains of variables were incorporated which have been shown to be associated with depression in the elderly [7]. All these factors are also associated with medication use (results not shown) and hence included in the analysis. These domains are: age, sex, urbanicity, socioeconomic status, physical health, social and interpersonal support, comorbidity with other psychiatric disease and personality.

For the analysis age was dichotomised in 10-year strata. Socioeconomic status is represented by level of education. The presence of physical disease was assessed using self-reported data, and cross-checked with GP-records [18]. Functional limitations were measured using a scale previously validated in the Netherlands [19, 20]. As a measure of cognitive functioning, the Mini Mental State Examination (MMSE [21]) was used. Van Tilburg [10] described how to measure characteristics of the network, such as partner status, the size of the social network and the amount of instrumental and emotional support exchanged with network members.

For the analysis, these continuous variables were dichotomised with a cut-off at the 50th percentile. A measure of mastery [22] was included as a cognitive psychological trait marker of personality. These procedures resulted in the construction of the dichotomous variables as shown in Table 1.

#### Data analysis

Bivariate association of depression with medication use was assessed by calculating odds ratios with 95% confidence levels. For all medication with statistically significant associations with depression, all associations with the other correlates of depression represented by the above-mentioned dichotomous variables were assessed. Logistic regression modelling was used to adjust for confounding. In all analyses conventional levels of statistical significance were used (p < 0.05). The statistically significant associations between depression and medication were adjusted for those correlates significantly associated with that medication.

The quantitative significance of selected groups of medication is illustrated by the Population Attributable Risk percentage (PAR%) [23]. The PAR% is that part of depression in the population that is associated with use of certain medication. Extra attention has been paid to the association between depression and β-blockers, with or without the interaction with cardiovascular disease.

#### Results

**Study sample**

The prevalence of depression and the associations with risk factors within the LASA population were reported in detail elsewhere [7]. Table 1 summarises the characteristics of the study sample. The high number of older old and older men is a result of the stratified sampling procedure. The prevalence of physical illness, functional disability and cognitive decline is within the expected range and shows that important variables are well represented.

Nine hundred and forty-five (35.7%) subjects did not use any medication. The remaining 1701 (64.3%) used