Psychotropic drug use in a group of Dutch nursing home patients with dementia: many users, long-term use, but low doses

Introduction
Dementia is a progressive disease. The main symptoms are memory dysfunctions, disturbances of judgement, and, at a later stage, aphasia, agnosia, and apraxia [1,2]. In addition, 'non-cognitive' or behavioural symptoms are often observed, such as personality disorders, delusions, or depression [2]. Behavioural disturbances can be a major source of distress and a burden for patients and/or their caregivers. Sometimes patients have to be institutionalized in a nursing home because of serious behavioural disturbances.

Dutch psychogeriatric nursing homes offer an environment that is tolerant of behavioural problems. A multidisciplinary team including a specially trained 'Dutch nursing home doctor' generates an individual management plan to approach this problematic behaviour. Psychotropic drugs are only prescribed if these approaches are no longer effective. Our investigation has shown behavioural disturbances in 70% of a group of nursing home patients with dementia. Agitation, negativism, depression, anxiety, psychosis, and aggression were most frequently observed. If there is a need for pharmacotherapeutic intervention, neuroleptics, benzodiazepines, and antidepressants have an important role in the alleviation of these symptoms [3].

There are few data available about the prescription of psychotropic drugs in Dutch nursing homes. Data indicate that 28-41% of the patients are treated with psychotropics [4], of which 27-31% are treated with neuroleptics [5-7], 8-22% with benzodiazepines [6-8], and 2-7% with antidepressants [7]. Data from international literature indicate that 26-87% of patients suffering from dementia are treated with at least one psychotropic drug [9-13]. Neuroleptics are prescribed in 12-47% of patients [6 7 10-15], benzodiazepines in 9-24% of patients [10-13], and antidepressants in 7-11% of patients [10-13].

Elderly people, and in particular those who suffer from dementia, are very susceptible to the side-effects of psychotropics and this warrants reservation in prescription. A high percentage of patients are reported to experience side-effects of neuroleptics such as sedation, extrapyramidal symptoms, and postural hypotension [6 12 16-19].

In 1984 doctors of "Joachim en Anna" nursing home developed a protocol for the rational prescription of neuroleptics [20]. On the basis of receptor–antagonism profiles, five relatively 'safe' neuroleptics were chosen [20]. Haloperidol was proposed as the drug of first choice for the treatment of psychotic behaviour (delusions and hallucinations) with agitation. Bromperidol was prescribed for the treatment of psychosis without agitation, and pimpernere for the treatment of aggression, negativism, and disturbances of diurnal rhythm. Zuclopenthixol was prescribed for the treatment of so-called 'aspecific' behavioural disturbances (mostly combi-

Keywords
- Adverse effects
- Dementia
- Drug utilization
- Nursing homes
- Pharmacoepidemiology
- Psychotropic drugs

Abstract
The aim of this study was to describe the use of psychotropic drugs in a psychogeriatric nursing home, "Joachim en Anna", in Nijmegen, the Netherlands. To this end the medical records of 890 nursing home patients with dementia, admitted between 1980 and 1989, were analysed retrospectively. Each time pattern of psychotropic drug use was registered. Drugs were coded by means of the Anatomical Therapeutic Chemical classification system. The daily dose was expressed as the ratio of the mean prescribed daily dose and the defined daily dose. Side-effects and changes in prescription patterns throughout the years were determined. Each analysis was performed retrospectively. A total of 3,090 time patterns of exposure to psychotropics were registered. Neuroleptics, benzodiazepines, and antidepressants accounted for 58, 32, and 9% of the time patterns, respectively. For almost every drug prescription the prescribed daily dose was lower than the defined daily dose. More than 75% of these nursing home patients had at least one prescription for a psychotropic drug during institutionalization. One or more side-effects were observed in 50% of the patients who used a neuroleptic. The total number of patients receiving psychotropics did not change throughout the study. Psychotropics were prescribed for long-term use, but in a low dose. Side-effects were frequently observed while the correct individual dose was being determined.

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nations of psychosis, aggression, anxiety, and negativism) and dehydrobenzperidol for interventions of short duration, for example, to prepare patients for invasive treatments like catheterization [20]. In 1990 this schedule was evaluated, with special attention being paid to efficacy and side-effects [6]. The current study addressed, in detail, the prescription of neuroleptics, benzodiazepines, and antidepressants, and changes in prescription patterns during the last 12 years. The aim of the study was to assess the use of psychotropic drugs in this nursing home with regard to the type of drug, the number of patients treated, the duration of use and dosage, changes in these aspects of psychotropic drug use between 1980 and 1992, and the prevalence of side-effects.

Methods

Patients
The study was a retrospective analysis of medical records. All patients with dementia according to DSM-III-R criteria [1] who were admitted to the “Joachim en Anna” nursing home in Nijmegen, the Netherlands, between 1 January 1980 and 31 December 1989 were included in the study. Follow-up data were collected until death or the end of the registration period in April 1992. Methods of data collection have been described previously [21 22].

“Joachim en Anna” is a nursing home with 250 beds. Most patients suffer from dementia. All patients are initially admitted on the same ward. In the first 6 weeks of institutionalization a full medical and neuropsychological examination is carried out. Afterwards patients are referred to one of the long-stay wards, where patients with a similar stage of dementia live together.

Psychotropic drug use
Psychotropic drug use was continuously registered from the day of admission. Data were obtained from the medication list of the medical record. Each time pattern (time window or risk window) of drug exposure, including one single dosage, was registered [23-25]. A time pattern of drug exposure was defined as an uninterrupted period of usage of the same drug. A change of dose between times was not considered a new time pattern.

Drugs were classified by means of the Anatomical Therapeutic Chemical (ATC) classification system [26]. The ATC system uses five levels of classification. The first, second, and third levels refer to an anatomical group with two therapeutic subgroups. The fourth level refers to the chemical/therapeutic subgroup, and the fifth level refers to the active component [26]. For example, the code N05AFO5 stands for zuclopenthixol. In this study we used the fourth level. Drug dosages were expressed according to the defined daily dose (DDD) methodology recommended by the WHO Drug Utilization Research Group for pharmacoepidemiological research [27]. In addition (mean) actual prescribed doses were recorded (PDD) and the ratio PDD to DDD was calculated. A PDD/DDD ratio < 1 indicates that the drug is prescribed in a lower dosage than recommended; a ratio > 1 indicates that the prescribed dosage is higher than recommended. For example, the DDD for haloperidol is 8 mg per day. When a mean of 2 mg per day is prescribed, the PDD/DDD ratio is 0.25. Furthermore whether a drug was withdrawn or continued at admission or whether the drug was administered during institutionalization was recorded.

Side-effects mentioned in the medical records were classified with the International Classification of Health Problems in Primary Care (ICPPC)-2-defined [28]. The code 9952 (side-effect medical agent correctly administered in proper dosage) was supplemented with codes for medication group and type of side-effect [28].

To investigate changes in psychotropic prescription time patterns throughout the time patients were admitted, it was studied whether the prescription of neuroleptics after 1984 was consistent with the protocol. Changes in the percentage of patients treated and in the duration of usage were investigated by dividing the study population into 10 cohorts (one cohort for each year). For a proper comparison, figures were corrected for the time that patients spent in the nursing home. Changes were studied by means of linear regression analysis [29].

Results
During the study period 890 patients with dementia were admitted to the nursing home, of whom 102 survived until April 1992; 70% of the patients were women. The mean time spent in the nursing home was 2.2 years, with a range from 0 to 10.6 years.

A total of 3,294 time patterns of psychotropic drug exposure were registered. 204 drugs were withdrawn on the day of admission. Therefore this study is based on the 3,090 remaining time patterns. A mean of 4.5 time patterns per user was registered (range 1-35 time patterns per user). In Table 1, the number of time patterns, the mean duration of drug exposure, the mean daily dose, and the PDD/DDD ratio are listed for the drugs that were actually administered during institutionalization (3,090 time patterns). Neuroleptics, benzodiazepines, and antidepressants accounted for 58, 32, and 9% of the time patterns, respectively. Because time patterns vary in duration, these percentages do not give valid information about the contribution of neuroleptics, benzodiazepines, and antidepressant to the prescribing pattern.

The nine most frequently prescribed drugs were zuclopenthixol, haloperidol, pipamperone, oxaze-
pam, nitrazepam, lormetazepam, trazodone, amitriptyline, and doxepin (Table 1). These covered about 70% of all time patterns prescribed. For almost all drugs the mean PDD was much lower than the DDD. For neuroleptics 25% of the DDD was prescribed, while for benzodiazepines and antidepressants this was 50% and 33%, respectively (Table 1).

During institutionalization more than 75% of the study population received one or more psychotropics (Table 2). Most patients were treated with a neuroleptic, 50% of the patients received a benzodiazepine, and 20% received an antidepressant. Also combinations of medications were frequently prescribed. A neuroleptic in combination with a benzodiazepine was administered in 252 patients. 142 patients received two neuroleptics at the same time (Table 2).

In general, psychotropics were prescribed for a long period. The median duration of the time patterns was 245 days. It has to be noted that a time pattern was ended when a patient died or when the registration period ended. More than 50% of the users of psychotropic drugs had a time pattern of drug exposure for 50 to 100% of their time spent in the nursing home.

More side-effects were associated with the use of neuroleptics than with the use of benzodiazepines or antidepressants (Table 3). One or more side-effects were observed in 50% of the patients who used neuroleptics. Excessive sedation was the most frequently reported problem in the medical records.

After 1984, a neuroleptic that was not included in the schedule was prescribed only thirteen times. Drugs such as levomepromazine, propricapizine, thiouridazine, alimemazine, promazine, perazine, and chlorpromazine almost totally disappeared from the prescription list.

Neither the total percentage of psychotropic drug used (expressed as neuroleptics, benzodiazepines, and antidepressants) nor the duration of usage changed throughout the time patients were admitted. Most figures showed fluctuations without a statistically significant rising or falling trend.

**Discussion**

At any time during institutionalization in this nursing home, more than 75% of the patients with dementia were prescribed a psychotropic drug. Neuroleptics

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Number of time patterns</th>
<th>Mean duration (days)</th>
<th>Mean dose (mg)</th>
<th>Mean PDD/DDD ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuroleptics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>600</td>
<td>135</td>
<td>5.4</td>
<td>0.18</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>330</td>
<td>123</td>
<td>1.5</td>
<td>0.19</td>
</tr>
<tr>
<td>Pipamperone</td>
<td>291</td>
<td>149</td>
<td>33.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Alimemazine</td>
<td>179</td>
<td>146</td>
<td>24.0</td>
<td>0.80</td>
</tr>
<tr>
<td>Bromperidol</td>
<td>124</td>
<td>153</td>
<td>1.4</td>
<td>0.14</td>
</tr>
<tr>
<td>Dehydrobenzperidol</td>
<td>105</td>
<td>85</td>
<td>4.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Properciazine</td>
<td>62</td>
<td>94</td>
<td>13.4</td>
<td>0.27</td>
</tr>
<tr>
<td>Sordinol</td>
<td>44</td>
<td>119</td>
<td>12.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>21</td>
<td>112</td>
<td>57.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Perazine</td>
<td>17</td>
<td>42</td>
<td>53.6</td>
<td>0.54</td>
</tr>
<tr>
<td>Promazine</td>
<td>12</td>
<td>101</td>
<td>52.2</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>497</td>
<td>130</td>
<td>15.8</td>
<td>0.32</td>
</tr>
<tr>
<td>Temazepam</td>
<td>210</td>
<td>101</td>
<td>11.8</td>
<td>0.59</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>137</td>
<td>136</td>
<td>1.0</td>
<td>1.01</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>90</td>
<td>129</td>
<td>4.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Diazepam</td>
<td>50</td>
<td>46</td>
<td>10.9</td>
<td>1.08</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>112</td>
<td>176</td>
<td>109.9</td>
<td>0.37</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>56</td>
<td>160</td>
<td>33.5</td>
<td>0.45</td>
</tr>
<tr>
<td>Doxepin</td>
<td>51</td>
<td>190</td>
<td>25.8</td>
<td>0.26</td>
</tr>
<tr>
<td>Mianserin</td>
<td>47</td>
<td>163</td>
<td>19.7</td>
<td>0.33</td>
</tr>
<tr>
<td>Mapritilene</td>
<td>10</td>
<td>545</td>
<td>51.4</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Not listed are levomepromazine, sulpiride, chlorpromazine, chlorprothixene, flurazepam, chlordiazepoxide, flunitrazepam, lorazepam, nomifensine, clomipramine, imipramine, lithium carbonate, and promethazine. These medications were each prescribed less than 10 times.
Table 2  Number of patients treated with neuroleptics, benzodiazepines, and antidepressants, parallel prescriptions*, and median duration of exposure expressed in days

<table>
<thead>
<tr>
<th>Patients (n = 890)</th>
<th>Median duration of exposure (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>At least 1 time pattern for a psychotropic</td>
<td>683</td>
</tr>
<tr>
<td>At least 1 time pattern for a neuroleptic</td>
<td>554</td>
</tr>
<tr>
<td>At least 1 time pattern for a benzodiazepine</td>
<td>456</td>
</tr>
<tr>
<td>At least 1 time pattern for an antidepressant</td>
<td>199</td>
</tr>
</tbody>
</table>

**Parallel prescription**

- 2 neuroleptics: 142 (16) 57
- 2 benzodiazepines: 45 (5) 33
- 2 antidepressants: 6 (1) 55
- 1 neuroleptic + 1 benzodiazepine: 252 (28) 84
- 1 benzodiazepine + 1 antidepressant: 74 (8) 36
- 1 neuroleptic + 1 antidepressant: 91 (10) 56
- 1 neuroleptic + 1 benzodiazepine + 1 antidepressant: 3 (4) 27

* Parallel prescription means that one or more drugs were prescribed at one time.

were most frequently prescribed, followed by benzodiazepines and antidepressants. Psychotropic drugs usually were prescribed for long-term use but in a relatively low dose. All these figures reflect the prescribing policy of one team of Dutch nursing home doctors. Therefore the results cannot be generalized to all Dutch nursing home patients.

The results are difficult to compare with international data. In this study, data were registered continuously, while most other studies have a cross-sectional design. Most studies do not report dosage and duration of use. The fact that the PDD was much lower than the internationally agreed DDD can be explained by the advanced age of these nursing home patients. Changes in pharmacodynamics and pharmacokinetics in elderly people increase the risk of cumulation and therefore the dosage has to be adjusted [30]. In addition, elderly people, and especially those with an organic brain syndrome, have a higher end-organ sensitivity for psychotropic drugs [30]. These and other mechanisms account for most of the observed side-effects. In particular, neuroleptics caused side-effects which led to adjustment of the dose or even withdrawal of the drug. It has to be mentioned that patients were not systematically checked for signs of sedation, extrapyramidal signs, or other symptoms. Therefore the figures reported here are most likely an underestimation of the real frequency and only express the recognized side-effects.

Neuroleptics can be effective in very low doses [6 17]. Willekens-Bogaers and coworkers found in their evaluation study that in 69% of their patients, who were also included in our investigation, psychosis, and/or behavioural disturbances could be reduced to an acceptable level [6]. This agrees with the finding of Schneider and coworkers. They concluded in their meta-analysis that neuroleptics were of benefit to

Table 3  Percentage of patients showing side-effects of antidepressants (n = 556), neuroleptics (n = 457), and benzodiazepines (n = 199)

<table>
<thead>
<tr>
<th>Side-effect*</th>
<th>Antidepressants</th>
<th>Neuroleptics</th>
<th>Benzodiazepines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>41</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Gait disorder</td>
<td>5</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Falling</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Extrapyramidal signs</td>
<td>9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cardiovascular problem</td>
<td>3</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Paradox reactions</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>15</td>
<td>14</td>
</tr>
</tbody>
</table>

* More than one side-effect could be observed per patient.
59% of patients with dementia; however, 41% of patients also improved on placebo therapy [31]. There are few studies about the efficacy of benzodiazepines or antidepressants in patients with dementia [32]. It is clear that doctors and nursing staff play an important role in judging the effects of psychotropics. In a nursing home, the tolerance of disturbing behaviour is high. Therefore better outcomes are probably achieved than with treatment given at home. Psychotropic drugs have to be administered in a dynamic way. In the search for the correct dose, the motto is "start low and go slow" [20]. The correct dose has to be determined on the basis of efficacy and side-effects (titration method). Therefore psychotropic drug prescription has to be accurately monitored by the (nursing home) doctor. Former investigations showed that psychotropic drug use can be reduced when a patient is admitted to a nursing home [33]. During institutionalization, however, drug use increases but after 2 years a steady decrease has been noted [34]. The high number of time patterns per patient and the wide range in these patterns reflect a continuous search for the right and most effective drug. The frequent changes of type of drugs can be explained by our impression that more symptoms change with time. Therefore psychotropic drug prescription has to be exponentially increased but after 2 years a steady decrease has been noted [34].

The prescription of combinations of drugs may indicate the complexity of symptomatic treatment of behavioural problems in these patients. Prescription of a neuroleptic in combination with a benzodiazepine can be a rational choice for treatment of agitation in the daytime and sleep disturbance during the night. But prescription of two neuroleptics at one time indicates difficulties in managing behaviour. When there is a need for dopamine as well as serotonin receptor antagonism, treatment with two neuroleptics can be a rational therapy. Recent studies show that extrapyramidal side-effects can be reduced by using these combinations of drugs [35 36]. In clinical practice, however, treatment outcomes are not always satisfying, so sometimes trial-and-error methods have to be used.

This investigation did not find any statistically significant changes in drug prescription patterns throughout the years patients were admitted. This finding is in contrast with our impression that more patients with serious behavioural disturbances have been admitted in the last years. Patients with Alzheimer's disease without behavioural problems can stay at home either with intensive home care or with day care if they live in residential homes. However, an increase in behavioural disturbances does not necessarily have to result in the prescription of more psychotropic drugs.

Conclusion

Despite a tolerant setting and multidisciplinary therapeutic approach, most of the patients in this psychogeriatric nursing home manifested behaviour for which psychotropics were prescribed. Psychotropics were prescribed for a long period but in a relatively low dosage. Side-effects were frequently observed during the search for the correct dosage.

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