Prevalence of anti-parkinson drugs' use in Ferrara, Northern Italy, 1988


Introduction - The period prevalence rate for anti-parkinson drugs (APD) use was reported in the Local Health Service of Ferrara (USL 31), Northern Italy, in 1988 (resident population: 177,000 inhabitants).

Material and methods - The study was performed through the analysis of the complete list of APD prescriptions in the USL 31 area provided by the computerized archives of USL 31 and the identification code of the patients which is unique for each resident of USL 31. The patients treated with neuroleptics known to be potential parkinsonism-inducing drugs were excluded.

Results - The period prevalence rate for APD users was 456.9 per 100,000 population. The prevalence rate for dopa derivatives users was 391.3 per 100,000. The prevalence did not vary between rural and urban zones of USL 31 both for APD and dopa derivatives users. A higher prevalence was obtained in a small rural commune of USL 31 both for APD users (758.5 per 100,000) and dopa derivatives users (718.6 per 100,000) than in the other 4 communes in which the study area is subdivided.

Conclusion - The reported prevalence could provide information on the occurrence of most parkinsonisms in the study area and some suggestions on the role of possible environmental factors.

The data on the occurrence of Parkinson’s disease (PD) show quite variable crude prevalence rates ranging from 84 to 187 per 100,000 population (1). Although this variability, together with the results of studies on twins (2), may suggest a major role for environmental conditions in the causal process, they could reflect differences in methodology as far as case collection, case selection and ascertainment are concerned (3). A recent descriptive survey in the area of the Local Health Service of Ferrara, Northern Italy, found a crude prevalence rate of 164.7 per 100,000 population on December 31st, 1988 (4). The case collection was performed through the study of all the possible sources of potential case material, a successive record linkage and the use of the diagnostic criteria for idiopathic PD (5). In the same survey the PD incidence was higher in the rural zone and among agricultural workers of the study area, leading the authors to suggest a possible causal role of environmental factors linked to agriculture.

A different methodological approach to obtain information on PD occurrence is based on the study of anti-parkinson drugs (APD) consumption (6, 7) in a given area. Since all drug prescriptions in Italy are recorded it is possible that an estimation of the prevalence of APD users in a geographical area could supply information about the occurrence of most parkinsonisms and not only idiopathic PD. Therefore, the epidemiological investigation in the area of the Local Health Service of Ferrara, Northern Italy, has been pursued through the estimation of the prevalence of APD users in the year 1988 to obtain results comparable with the previous descriptive study on PD (4).

Material and methods

Study area. Italy is subdivided into Local Health Services, Unità Sanitarie Locali (USL), which have similar socio-economic characteristics and medical facilities. The Local Health Service of Ferrara, Unità Sanitaria Locale n. 31 (USL 31), in the region of Emilia Romagna, Northern Italy, covers a flat area of 724 square kilometers in the central part of the province of Ferrara. The resident population decreased, during the study period from January 1st,
1988 to December 31st, 1988, from 177083 to 176621 inhabitants with an average of 176852 (93373 females, 83478 males). This population is of mixed Mediterranean and Central European descent and, considering the HLA gene frequencies, it has been shown to be typically caucasian (8).

The migratory flux from and into the USL 31 area is really low. The resident population lives mainly in the urban areas of the communes (the commune is the smallest local political division of Italy governed by a mayor and municipal council) of Ferrara and Bondeno (at the time of the study about 120000 individuals). The other three communes of the USL 31 area (Vigarano Mainarda, Poggio Renatico, Mastorello), with centers of under 5000 inhabitants, are predominantly rural.

The standard of living and medical organization are reasonably high. Only some rural houses use untreated natural water sources whereas the majority of the population uses aqueduct water. At the Italian general census of 1981 the active working population was about 76000 individuals (43%) generally employed in small and medium industries and in agriculture as well as commerce, transportation, services and public administration. This situation only partially reflects the traditional economy of the study area which is mainly oriented to agricultural activities: in fact, following the Italian national development programs enacted after World War II, the industrialization of the area of Ferrara has been a relatively recent phenomenon.

Statistical analysis —The confidence interval (CI) of the observed rates was determined as a proportion of N, based on the Poisson distribution (10). The comparison between rates was performed using the chi-square test.

The crude rates were adjusted by age to the Italian population at the general census of 1981 using the direct method (11). The comparison between two age-adjusted rates was performed estimating the variance of the difference between the two directly standardized rates and the z value (12).

The crude rates reported in the 5 communes of the study area were also age-adjusted by indirect method using the whole resident population of the study area as standard population (11).

Results

The number of individuals who received APD prescriptions in the USL 31 area during the study period amounted to 1010. From this number patients not residing in the USL 31 area and the subjects who received less than three prescriptions of APD during 1988 (not continuous APD users) were excluded. Moreover, a few young women (younger than 40 years) with prescriptions of only bromocriptine were excluded because they were not likely affected by neurological disorders. Therefore, the final number of continuous APD users was 808 (484 women, 324

Fifteen APD available on the Italian market, corresponding to 24 proprietary preparations, were considered for the study according to the Anatomic Therapeutic Chemical Classification of Drugs recommended by the World Health Organization (9). Therefore, the main therapeutic group, NO4 — antiparkinson drugs, was considered; it includes the therapeutic sub-groups NO4A — anticholinergic agents (NO4AA — tertiary amines with carbon chain, NO4AB — ethers chemically close to antihistamines) and NO4B — dopaminergic agents (NO4BA — dopa and dopa derivatives, NO4BB — adamanthane derivatives, NO4BC — dopamine agonists, NO4BD — monoamine oxidase type b inhibitors).

With the aim of excluding the patients affected by drug-induced parkinsonism the individuals who, during 1988, received both prescriptions of anticholinergic agents and neuroleptics known to be potential parkinsonism-inducing drugs (main therapeutic group NO5 — psycholeptics with reference to the therapeutic sub-groups NO5AA, NO5AB, NO5AC — phenotiazines, NO5AD — butyrophenone derivatives, NO5AF — thioxanthene derivatives, NO5AG — diphenylbutylpiperidine derivatives, NO5AH dibenzodiazepine and dibenzoazepine derivatives, NO5AL — benzamides, NO5AN — lithium) were not selected.

Case collection —At the time of the study the Italian National Health Service (INHS) supplied the whole population with APD and the sales data were collected in the USL (the local agency of the INHS) data-banks for financial purposes. Since each resident of Italy received free care through the INHS and APD were provided almost free of charge through the USL, the list of APD prescriptions of the USL represented virtually 100% of the APD sales in the corresponding geographical area. Therefore, the source of case collection was the complete list of APD prescriptions in the USL 31 area during the time period from January 1st, 1988 to December 31st, 1988 obtained by the computerized archives of USL 31. The list provided the name of the prescribed APD, the date of APD sale, the name and the INHS identification code of the patient (which is unique for each resident of the USL 31) and the name and identification code of the physician who prescribed the APD. Only the authors of the present study consulted the APD prescriptions list: all the authors are qualified doctors and therefore obliged to professional secrecy. The INHS identification code provided information on the age and the residence of the patients.
The prevalence for dopa derivatives users was 400.7 per 100000 in the urban zone of USL 31 (280.7 per 100000 when age-adjusted) and 371.2 per 100000 in the rural zone (263.6 per 100000 when age-adjusted), a not significant difference.

The prevalence rate reported for APD users in the 5 communes of the USL 31 area was not completely uniform (Table 3): the highest rate was found in the rural commune of Masi Torello and it was significantly higher than the overall rate obtained in the other 4 communes (452.5 per 100000) ($X^2 = 5.08; 0.01 < p < 0.025$). None of the rates reported in the other communes was significantly different from the overall rate found in the other 4 communes. When only the other 4 communes than Masi Torello were compared a homogeneous prevalence was found (the comparison of each of them versus the other three was never significant). The only significant comparison between two communes was Masi Torello versus Vigarano Mainarda (where the lowest rate was found) ($X^2 = 6.21; 0.01 < p < 0.025$). When the age-adjusted rates by direct method were compared the difference between Masi Torello and the other 4 communes considered as a whole (317.2 per 100000) was confirmed as statistically significant ($z = 3.13; 0.001 < p < 0.005$) as well as the difference between Masi Torello and Vigarano Mainarda ($z = 2.74; 0.005 < p < 0.01$). Using the resident population as standard population the indirect method of age-adjustment was applied to obtain the standardized ratio (SR) for each commune: the largest difference was found in the commune of Masi Torello (SR = 1.69).

When only dopa derivatives users were taken into consideration a similar variation of prevalence among the 5 communes of USL 31 area was found (Table 4): the highest rate was reported in the small commune of Masi Torello and the only significant comparison was Masi Torello versus the other 4 communes considered as a whole (386.6 per 100000) ($X^2 = 6.98; 0.005 < p < 0.01$). The prevalence was homogeneous in the other 4 communes than Masi Torello. The only significant comparison between two communes

### Table 1. Anti-parkinson drugs users in the USL 31 of Ferrara, Northern Italy, in 1988 by therapeutic group

<table>
<thead>
<tr>
<th>Therapeutic group</th>
<th>Number of users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopa and dopa derivatives</td>
<td>692 (85.6%)</td>
</tr>
<tr>
<td>Dopa</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Dopa + decarboxylase inhibitor</td>
<td>690 (85.4%)</td>
</tr>
<tr>
<td>Other anti-parkinson drugs (one or more)</td>
<td>116 (14.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>808*</td>
</tr>
</tbody>
</table>

* 304 patients (37.6%) were treated with dopa derivatives + other anti-parkinson drugs (one or more).

### Table 2. Age- and sex-specific period prevalence rate of anti-parkinson drugs users in 1988 in the area of USL 31 of Ferrara, Northern Italy

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Women</th>
<th>Men</th>
<th>Both sexes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Rate/100000</td>
<td>No. of cases</td>
</tr>
<tr>
<td>30–39</td>
<td>12</td>
<td>103.2</td>
<td>10</td>
</tr>
<tr>
<td>40–49</td>
<td>20</td>
<td>159.0</td>
<td>24</td>
</tr>
<tr>
<td>50–59</td>
<td>30</td>
<td>279.6</td>
<td>35</td>
</tr>
<tr>
<td>60–69</td>
<td>102</td>
<td>854.1</td>
<td>79</td>
</tr>
<tr>
<td>70–74</td>
<td>84</td>
<td>1259.6</td>
<td>120.0</td>
</tr>
<tr>
<td>&gt;75</td>
<td>228</td>
<td>2259.5</td>
<td>119</td>
</tr>
<tr>
<td>Total</td>
<td>484</td>
<td>518.3</td>
<td>324</td>
</tr>
</tbody>
</table>

The prevalence for dopa derivatives users was 400.7 per 100000 in the urban zone of USL 31 (280.7 per 100000 when age-adjusted) and 371.2 per 100000 in the rural zone (263.6 per 100000 when age-adjusted), a not significant difference.

The prevalence rate reported for APD users in the 5 communes of the USL 31 area was not completely uniform (Table 3): the highest rate was found in the rural commune of Masi Torello and it was significantly higher than the overall rate obtained in the other 4 communes (452.5 per 100000) ($X^2 = 5.08; 0.01 < p < 0.025$). None of the rates reported in the other communes was significantly different from the overall rate found in the other 4 communes. When only the other 4 communes than Masi Torello were compared a homogeneous prevalence was found (the comparison of each of them versus the other three was never significant). The only significant comparison between two communes was Masi Torello versus Vigarano Mainarda (where the lowest rate was found) ($X^2 = 6.21; 0.01 < p < 0.025$). When the age-adjusted rates by direct method were compared the difference between Masi Torello and the other 4 communes considered as a whole (317.2 per 100000) was confirmed as statistically significant ($z = 3.13; 0.001 < p < 0.005$) as well as the difference between Masi Torello and Vigarano Mainarda ($z = 2.74; 0.005 < p < 0.01$). Using the resident population as standard population the indirect method of age-adjustment was applied to obtain the standardized ratio (SR) for each commune: the largest difference was found in the commune of Masi Torello (SR = 1.69).

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was Masi Torello versus Vigaran Mainarda (where the lowest rate was found) \((X^2 = 6.91; \ 0.005 < p < 0.01)\). The comparison of the age-adjusted rates by direct method confirmed the difference between Masi Torello and the other 4 communes (overall rate 270.7 per 100 000 \((z = 2.56; \ 0.01 < p < 0.025)\) and between Masi Torello and Vigaran Mainarda \((z = 2.97; \ 0.001 < p < 0.005)\). The SR obtained for each commune using the indirect method showed the largest difference in Masi Torello \((SR = 1.87)\).

**Discussion**

The prevalence for both APD and dopa derivatives users in the USL 31 exceeded the rate obtained for idiopathic PD in the same area and year (4) and that for the most part of caucasian populations (1). Since parkinsonism is by far the main indication for APD (13) it is likely that the present prevalence rate supplies information on the occurrence of many types of parkinsonism (idiopathic PD, secondary parkinsonism, parkinsonism plus syndromes – multiple system degenerations) that can be treated with APD. Therefore, the present prevalence could be considered suggestive of the occurrence of parkinsonism rather than only idiopathic PD in the USL 31. It is, however, difficult, at least in Italy, to obtain reliable data on the occurrence of all types of parkinsonism owing to the complexity of the study design and the various resources it involves when large study population is considered (money, time, research team, etc.). However, thanks to the excellent computerized archives of USL 31 and the system of drug prescription records, the number of all the APD users in a large study population was obtained in a short time with little expense in the course of the present study.

As shown by the previous survey on idiopathic PD (4) the age-adjusted rates by direct method to the general Italian population decreased from the crude figures. This phenomenon reflects the different age composition of the Northern Italy population (in which the average life duration is longer and the birth rate is lower) when compared to the Italian general population. However, also the age-adjusted rates seem to be quite high with reference to the data commonly reported in literature (1).

An alternative methodological approach has been used in the door-to-door surveys that generally estimated higher rates for PD (5, 14–16) than the figures commonly reported from caucasians. The door-to-door surveys are very rigorous from the methodological point of view but, owing to the high cost, they involve small study populations. However, it is interesting that the prevalence rates for all types of parkinson reported through door-to-door surveys in the Italian region of Sicily (15, 16) are similar to the rates estimated for APD and dopa derivatives users in USL 31 area. It is, therefore, possible that the present prevalence rates could reflect the parkinsonism occurrence in the study area. However, the present rates seem to be high when compared to the rates obtained in Scandinavia through the defined daily dose of dopa (146 per 100 000) (6) or another sophisticated mathematical model (167.9 per 100 000) (17). However, the present findings could be the result of a particular practice on the part of USL 31 physicians to prescribe APD especially for elderly people (2.2% of the resident subjects over 75 years of age were continuous users of APD).

With reference to the results of the previous study on idiopathic PD (4), of interest are the official data (18–22) on the high usage of pesticides and herbicides in the province of Ferrara given its traditional agricultural economy: in the years 1984–1986 the average consumption was 5590 g/hectare in the province of Ferrara versus a national average of 2374 g/hectare. Particularly high was the usage of paraquat (in the years 1984–1986 an average of 417 g/hectare versus a national average of 136 g/hectare), the herbicide similar to 1-methyl-1,2,3,6-tetrahydropyridine (MPTP), a well-known toxin that can cause parkinsonism (23). Moreover, the official data show high usage of other potential toxins such as fungicides like maneb and mancozeb, widely used in wood industries and paper-mills (in the years 1984–1986 in the province of Ferrara, which covers 0.9% of the Italian territory, an average of 289626 kg of maneb and mancozeb was used, about 6.3% of the Italian national consumption) (18–22). These fungicides are diethylene dithiocarbamates suspected to be potential parkinsonism-inducing toxins because they enhance the effect of MPTP in mice (24) and contain manganese that is linked to types of secondary parkinsonism (25, 26). Although other epidemiological surveys have shown higher risk for parkinsonism in association with rural residence and residence in zones with high consumption of herbicides and

### Table 4. Dopa derivatives users prevalence rate per 100000 population in the USL 31 of Ferrara, Northern Italy, in 1988 by commune of residence

<table>
<thead>
<tr>
<th>Commune of USL 31</th>
<th>Average population</th>
<th>No. of cases</th>
<th>Crude rate</th>
<th>Age-adjusted rate</th>
<th>Predirect method*</th>
<th>SR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrara</td>
<td>142859</td>
<td>551</td>
<td>385.7</td>
<td>271.2</td>
<td>0.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bondeno</td>
<td>17419</td>
<td>66</td>
<td>378.9</td>
<td>253.4</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V. Mainarda</td>
<td>6632</td>
<td>21</td>
<td>316.6</td>
<td>230.5</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. Renatico</td>
<td>7437</td>
<td>36</td>
<td>484.1</td>
<td>337.0</td>
<td>1.23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Torello</td>
<td>2505</td>
<td>18</td>
<td>718.6</td>
<td>580.9</td>
<td>1.87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Italian population at the general census of 1981 as standard population.

* Standardized ratio (resident population of USL 31 area as standard population).
pesticides or in zone close to wood industries, paper-mills or vegetable manufactures (6, 27–30) it would seem to be simplistic to attribute the high APD users prevalence found in USL 31 to the high usage of the above mentioned substances since unknown factors could be involved. Moreover, the present survey did not reveal any difference between rural and urban areas of USL 31 both for crude and age-adjusted rates.

The prevalence for both APD and dopa derivatives users was higher in the commune of Masi Torello than the other four communes of the USL 31 area. This higher prevalence rate found in Masi Torello, that is the commune of the study area with the smallest resident population, could reflect some specific practices in APD prescriptions by local physicians. However, it is interesting that the area of Masi Torello is traditionally known to be one of the most developed agricultural zone of the province of Ferrara (22) and the official data show that in 1981, in spite of a recent industrialization and the appearance of new professions, 41.9% of the active working population of the commune of Masi Torello was still employed in agriculture whereas the percentage for the whole USL 31 area was only 16.6% (Table 5).

Lower rates were reported in the other rural communes that have not strongly different economic activities from Masi Torello: for instance no evident reasons are known to justify the difference between Masi Torello and Vigarano Mainarda since they are both small predominantly rural communes.

In conclusion, the present study would seem to confirm only partially the data provided by the previous survey on idiopathic PD in the same area (4) showing only little suggestion of a higher risk for parkinsonism in the agricultural environment of USL 31.

Whereas in the previous survey (4), that selected only patients affected by idiopathic PD, a higher prevalence among men was found the present study shows a higher rate of APD users among women. However, the age-specific prevalence rates of APD users did not present any difference between sexes: in fact, the age-specific approach used in the present study corrected an artifact due to the fact that the female population in the study area is higher in the oldest groups (among the over 75 the number of resident women was almost twice that of men).

As in the previous study (4), the age-specific rates increased progressively with advancing age. Other studies have also found a progressive increase of PD prevalence up to over 90 s (31, 32). Moreover, the other surveys on APD consumption as well as the door-to-door surveys for both PD and parkinsonism have shown increasing prevalence rates with advancing age (17, 5, 16).

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References

Table 5. Active working population of the USL 31 of Ferrara, Northern Italy, according to commune of residence and occupational status (1981 general census)

<table>
<thead>
<tr>
<th>Commune</th>
<th>Active working population</th>
<th>Agriculture</th>
<th>Industry</th>
<th>Other activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrara</td>
<td>60608</td>
<td>8603 (13.3%)</td>
<td>17875 (29.5%)</td>
<td>34670 (57.2%)</td>
</tr>
<tr>
<td>Bondeno</td>
<td>7796</td>
<td>2049 (26.3%)</td>
<td>3275 (42.0%)</td>
<td>2472 (31.7%)</td>
</tr>
<tr>
<td>V. Mainarda</td>
<td>3081</td>
<td>933 (30.2%)</td>
<td>1209 (39.1%)</td>
<td>949 (30.7%)</td>
</tr>
<tr>
<td>P. Renatico</td>
<td>3447</td>
<td>1130 (32.9%)</td>
<td>1344 (38.0%)</td>
<td>973 (28.2%)</td>
</tr>
<tr>
<td>M. Torello</td>
<td>1133</td>
<td>475 (41.9%)</td>
<td>319 (28.8%)</td>
<td>339 (29.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>76075</td>
<td>12650 (16.6%)</td>
<td>24022 (31.6%)</td>
<td>38403 (51.8%)</td>
</tr>
</tbody>
</table>

* Commerce, transport, communications, public administration, services.


