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## The association between nervous system drugs and incidence of Amyotrophic Lateral Sclerosis

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## Introduction

The risk of Amyotrophic Lateral Sclerosis (ALS) has been found reduced among subjects with previous consumption of non-steroidal anti-inflammatory drugs (NSAID)<sup>1,2,3</sup>, although with mixed results, of Angiotensin-Converting Enzyme (ACE) inhibitors drugs<sup>4</sup>. Antipsychotics and antidepressants have been also hypothesized as protective agents from ALS onset<sup>5</sup>, even though no longitudinal studies have been conducted on the association between ALS and previous nervous system drugs consumption. Therefore, aim of the present study was to analyze the association between prescription of this class of drugs and subsequent risk of developing Amyotrophic Lateral Sclerosis in a large Italian urban population.

## Materials and methods

The study population was composed of all people present at 2001 Italian census, already resident in Turin (Italy) in 1996 (n=737,979). Census data were linked at the individual level with those of the Municipality Registry, of the ATC Drug Registry (available from 1997) and of the ALS Piedmont Regional Registry (available from 1996).

Subjects were followed-up from January 1<sup>st</sup> 2002 to October 8<sup>th</sup> 2014 (last ALS Registry update), while exposure to nervous system drugs was measured from 1997 until December 31<sup>st</sup> 2012 or until 1 year before the ALS onset. During the follow-up period, each subject contributed to person-years from start of follow-up until emigration out of town, death or end of follow-up.

Not all the families of nervous systems drugs were considered, on one hand because the Piedmont Registry includes only drugs prescribed through the National Health Service (NHS), on the other hand because of the small numbers of subjects who were prescribed drugs belonging to some families. Therefore, the association between ALS and drug prescriptions was explored for the following ATC families of nervous system drugs: opioids (N02A); anti-epileptic drugs (N03A); antiparkinson drugs (N04), including anticholinergic (N04A) and dopaminergic agents (N04B); antipsychotics (N05A); antidepressants (N06A).

Antiparkinson drugs were evaluated as a single category, because of the small number of exposed ALS cases for anticholinergic (n=1) and dopaminergic agents (n=6);

The association of ALS with nervous system drugs was estimated for ever exposure (at least one prescription of the corresponding drug family), as well as cumulative exposure in tertiles, using as the reference category subjects without prescriptions of the same drug family.

The outcome variable was represented by ALS onset, ascertained from the Regional ALS Registry.

The association between nervous system drugs consumption and ALS onset was estimated by

multivariate Poisson regression models, adjusted for age (as continuous), sex, education level (primary, secondary, higher and graduate education), marital status (married, unmarried and previously married, which included separated and divorced people) and prescription of other nervous system drug families.

## Results

The study population was composed of 737,979 subjects (46.9% males), of which 296 were diagnosed with ALS during the follow-up period, after exclusion of subjects diagnosed with ALS before start of follow-up. Annual incidence of ALS was 37.0 per million inhabitants.

In the analysis for ever exposure, opioids (IRR=0.17) and antiparkinson drugs (IRR=0.42) were significantly inversely associated with ALS risk, while for antidepressants the association was only marginally significant (IRR=0.79).

Examining cumulative exposure, the protective role of opioids was confirmed for all exposure categories (test for trend: p<0.001), whereas for antiparkinson drugs only a non-significant protective effect was present in the highest exposure category (IRR=0.23).

ALS was also significantly associated with cumulative exposure to antidepressants in the intermediate cumulative category (IRR=0.54), with a significant test for trend across dose categories (p=0.03).

## Conclusion

In conclusion, the present study revealed a protective effect of opioids and antidepressants on ALS onset, which is a novel finding, to our knowledge. The dose-response effect observed between ALS risk and cumulative exposure to these drug families indicates that these associations may reflect a causal relationship. The significant association found with ever exposure to antiparkinsons is also suggestive of a protective role of this drug family on ALS risk, although the number of exposed ALS cases was too small to draw any sound conclusion.

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Table. Incidence Rate Ratio (IRR) of ALS onset associated with nervous system drugs prescriptions distinguished by family (ATC), ever exposure (model 1) and categorical cumulative dose (model 2) – Poisson regression models adjusted for age, sex, education and marital status.

|   |   | Total pop. (%)                               | ALS pop. (%) | IRR              | 95% CI           |
|---|---|--|--------------|------------------|------------------|
| <b>Model 1</b>                            | <b>prescription of:</b>                   | <b>opioids (N02A)</b> 127,978 (17.3)         | 16 (5.4)     | <b>0.17</b>      | <b>0.10-0.28</b> |
|   |   | <b>antiepileptics (N03A)</b> 77,840 (10.5)   | 32 (10.8)    | 1.09             | 0.75-1.59        |
|   |   | <b>antiparkinsons (N04)</b> 25,759 (3.5)     | 6 (2.0)      | <b>0.42</b>      | <b>0.19-0.95</b> |
|   |   | <b>antipsychotics (N05A)</b> 63,210 (8.6)    | 23 (7.8)     | 0.82             | 0.53-1.28        |
|   |   | <b>antidepressants (N06A)</b> 196,150 (26.6) | 74 (25.0)    | <b>0.79</b>      | <b>0.60-1.04</b> |
| <b>Model 2</b>                            | <b>opioids (N02A)</b>                     | <b>no prescription</b> 610,001 (82.7)        | 280 (94.6)   | 1                | -                |
|   |   | <b>I tertile (up to 3)</b> 47,656 (6.5)      | 9 (3.0)      | <b>0.25</b>      | <b>0.13-0.49</b> |
|   |   | <b>II tertile (4 - 13)</b> 37,855 (5.1)      | 3 (1.0)      | <b>0.10</b>      | <b>0.03-0.35</b> |
|   |   | <b>III tertile (over 14)</b> 42,467 (5.7)    | 4 (1.4)      | <b>0.14</b>      | <b>0.05-0.39</b> |
|   | <b>antiepileptics (N03A)</b>              | <b>no prescription</b> 660,139 (89.5)        | 264 (89.2)   | 1                | -                |
|   |   | <b>I tertile (up to 6)</b> 26,208 (3.5)      | 16 (5.4)     | 1.15             | 0.69-1.91        |
|   |   | <b>II tertile (7 - 34)</b> 25,546 (3.5)      | 8 (2.7)      | 1.19             | 0.57-2.51        |
|   |   | <b>III tertile (over 35)</b> 26,086 (3.5)    | 8 (2.7)      | 1.25             | 0.58-2.67        |
|   | <b>antiparkinsons (N04)</b>               | <b>no prescription</b> 712,220 (96.5)        | 290 (98.0)   | 1                | -                |
|   |   | <b>I tertile (up to 14)</b> 8,792 (1.2)      | 2 (0.7)      | 0.38             | 0.09-1.55        |
|   |   | <b>II tertile (15 - 63)</b> 8,213 (1.1)      | 3 (1.0)      | 0.73             | 0.22-2.41        |
|   |   | <b>III tertile (over 64)</b> 8,754 (1.2)     | 1 (0.3)      | 0.23             | 0.03-1.60        |
|   | <b>antipsychotics (N05A)</b>              | <b>no prescription</b> 674,769 (91.4)        | 273 (92.2)   | 1                | -                |
|   |   | <b>I tertile (up to 7)</b> 20,993 (2.9)      | 9 (3.0)      | 0.77             | 0.40-1.50        |
|   |   | <b>II tertile (8 - 39)</b> 20,776 (2.8)      | 7 (2.4)      | 0.99             | 0.43-2.26        |
| <b>III tertile (over 40)</b> 21,441 (2.9) |   | 7 (2.4)                                      | 1.24         | 0.51-3.00        |                  |
| <b>antidepressants (N06A)</b>             | <b>no prescription</b> 541,829 (73.4)     | 222 (75.0)                                   | 1            | -                |                  |
|   | <b>I tertile (up to 4)</b> 70,129 (9.5)   | 40 (13.5)                                    | 1.06         | 0.76-1.49        |                  |
|   | <b>II tertile (5 - 20)</b> 60,474 (8.2)   | 15 (5.1)                                     | <b>0.54</b>  | <b>0.31-0.92</b> |                  |
|   | <b>III tertile (over 21)</b> 65,547 (8.9) | 19 (6.4)                                     | 0.58         | 0.32-1.05        |                  |