# The anticholinergic cognitive burden of drugs in the REMIND cohort:

# a cross- sectional study in elderly people with cognitive complaints.

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# Background 1:
# Why studying medication with anticholinergic activity?

- Evidence are not conclusive to impute to drugs with a anticholinergic action a negative impact on cognition.

- Some studies demonstrate an association between anticholinergic use and worsening in cognitive performance of people[1,2,3,4].

- Some longitudinal observational studies[5,6] do not support this hypothesis.

1. Different definition of anticholinergic effect.
2. Different setting (primary care vs. hospital).
3. Different study design (cross-sectional vs. longitudinal cohort study).
4. Different aged of studied population.


References:

[1] *Carriere I. et al., Drugs with anticholinergic properties cognitive decline and dementia in general population. Arch internal medicine, 2009.*

[2] *Boutsani et al., "impact of anticholinergics on the aging brain: a review and practical application", aging health, 2008.*

[3] *Bottigi KA et al., "Long term cognitive impact of anticholinergic medications in older adults". Am J Geriatr Psychiatry, 2006.*

[4] *Cambpell N. et al., The cognitive impact of anticholinergics: a clinical review. Clin Interv Aging, 2009.*

[5] *Cambpell et al., use of anticholinergics and the risk of cognitive impairment in an African American population, Neurology, 2010.*

[6] *Whalley et al., "anticholinergic drugs in late life: adverse effects on cognition but not on progress to dementia", Journal of Alzheimer Disease, 2012*

# Background 2: The regulatory framework in Milan

RegioneLombardia

DECRETO N° 9942 Del 05/10/2009

Identificativo Atto n. 705

DIREZIONE GENERALE SANITA'

*Oggetto* DETERMINAZIONI IN MERITO ALL'ORGANIZZAZIONE IN RETE E CRITERI DI RICONOSCIMENTO DELLE STRUTTURE DEDICATE ALLE DEMENZE

Regione Lombardia

ASL Milano

Percorso Preventivo-Diagnostico-Terapeutico-Assistenziale Riabilitativo (PDTAR)
per la popolazione e i pazienti con demenza
(versione 20.10.2011)

# Background 3:

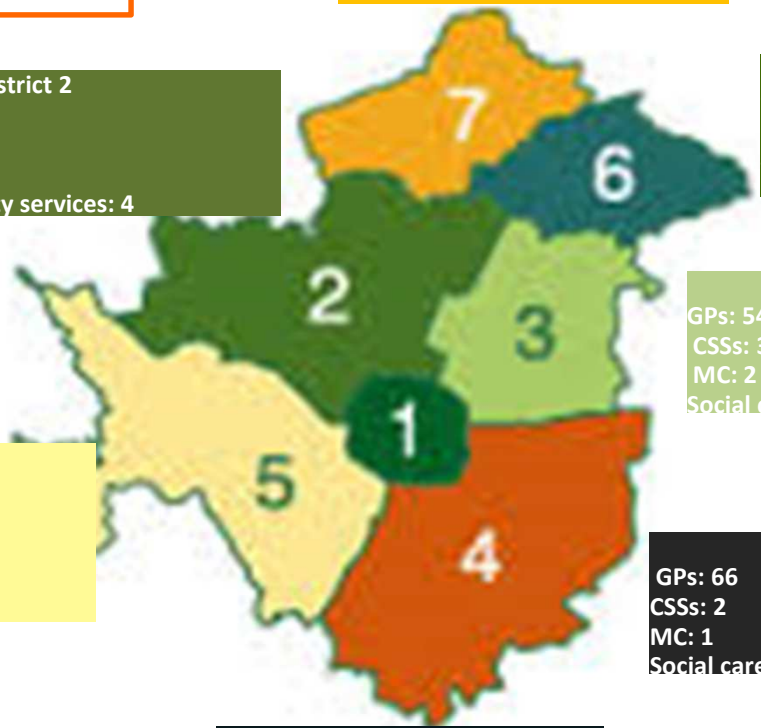

- The REMIND study, funded by the Ministry of Health and coordinated by the Istituto Carlo Besta of Milan, is a 3-year (2013-2015) population-based **pragmatic prospective cohort study.**

- To implement the PDTAR shared with GPs, Memory Clinics (MCs), Community-based Specialist Services (CSSs) and Social Care Community Services

- To evaluate the effectiveness of the PDTAR in promoting:
  - primary care prevention
  - appropriateness of patients' referral to specialists
  - timely diagnosis
  - coordination and integration of health and social care plan
  - optimization of resource allocation.

# Background 4 : the 7 districts in the Milan HA

**353 GPs, 14 MCs, 15 CSSs, 19 Social Care Community Services**




**District 7**
GPs: 35
MC: 1
Social care community service: 1

**District 2**
GPs: 73
CSSs: 4
MCs: 3
Social care community services: 4

**District 6**
GPs: 38
MC: 1
Social care community services: 2

**District 3**
GPs: 54
CSSs: 3
MC: 2
Social care community services: 5

**District 5**
GPs: 70
CSSs: 4
MCs: 5
Social care community services: 2

**District 4**
GPs: 66
CSSs: 2
MC: 1
Social care community services: 4

**District 1**
GPs: 16
CSSs: 2
MCs: 2
Social care community service: 1

# Aim of the present study

- To evaluate the use of drugs with anticholinergic properties in the cohort of the REMIND study.

# Method

- **Design**: Cross sectional study
- **Setting**: Primary care (353 GPs)
- **Enrolment**: April 2013- March 2014
- **Inclusion criteria**: 4246 consecutive subjects aged over 45 years with first cognitive complain (perceived by the subject and/or by a relative and/or by the GP) and living in Milan
- **Assessment:** clinical evaluation, drug history, MMSE performed by trained GPs
- **Outcome:** cognitive impairment as defined by a MMSE correct score <24

# The Anticholinergic Cognitive Burden (ACB) score [1]

| Score 1 | Score 2 | Score 3 |
|---|---|---|
| Aloperidolo | Amantadina | Amitriptilina |
| Alprazolam | Belladonna | Atropina |
| Atenololo | Carbamazepina | Clorfeniramina |
| Bromfeniramina | Ciclobenzaprina | Clorpromazina |
| Bupropione | Cyproeptadina | Clemastina |
| Captopril | Loxapina | Clomipramina |
| Clortalidone | Oxcarbazepina | Clozapina |
| Cimetidina | Pethidina | Desipramina |
| Clorazepate | Pimozide | Difenidramina |
| Codeina | | Idroxizina |
| Colchicina | | Imipramina |
| Coumadin | | Nortriptilina |
| Diazepam | | Olanzapina |
| Digossina | | Orphenadrina |
| Dipiridamolo | | Oxibutinina |
| Disopiramide | | Paroxetina |
| Fentanyl | | Perphenazina |
| Furosemide | | Prociclidine |
| Fluvoxamina | | Promazina |
| Idrocortisone | | Prometazina |
| Isosorbide | | Quetiapina |
| Loperamide | | Scopolamina |
| Metoprololo | | Tolterodina |
| Morfina | | Trifluoperazina |
| Nifedipina | | Trimipramina |
| Prednisone | | |
| Risperidone | | |
| Teofillina | | |
| Trazodone | | |

The ACB can be categorized as:

1. **no burden**, or **ACB 0** (receiving no drugs with ACB score of 1, 2, or 3),
2. **mild burden, or ACB 1** (receiving at least one drug with an ACB score of 1) and
3. **severe burden, or ACB 2** (receiving at least one drug with an ACB score of 2 or 3, or receiving more than 3 drugs with ACB score of 1).

*The original list was modified by excluding the drugs that are not actually marketed in Italy according to the Agenzia Italiana del Farmaco (http://www.agenziafarmaco.gov.it/) .*

*[1] Cai X et al., Alzheimer's and dementia, 2013*

# Tab. 1: Baseline characteristics of the whole sample of subjects and by ACB score

| | Tot N 4246 | ACB score 0 N 3152 | ACB score 1 N 927 | ACB score 2 N 167 | P |
|---|---|---|---|---|---|
| **Age** | | | | | **P< 0,0001** |
| ≤ 70 yrs, N (%) | 826 (19,5) | 683 (21,7) | 121 (13,1) | 22 (13,2) | |
| 71-80 yrs, N (%) | 1850 (43,6) | 1244 (39,5) | 338 (36,5) | 66 (39,5) | |
| > 80 yrs, N (%) | 1570 (37,0) | 1225 (38,9) | 468 (50,5) | 79 (47,3) | |
| Mean ± SD | 77 ± 8,2 | 76,4 ± 8,4 | 78,9 ± 7,4 | 78,4 ± 7,8 | **P< 0,0001** |
| Median (range) | 78 (45-100) | 77 (45-100) | 80 (51-99) | 79 (51-94) | |
| **Gender** | | | | | **P= 0,001** |
| Female, N (%) | 2821 (66,4) | 2066 (65,6) | 623 (67,2) | 132 (79) | |
| Male, N (%) | 1425 (33,6) | 1086 (34,5) | 304 (32,8) | 35 (21) | |
| **Education** | | | | | **P= 0,001** |
| ≤ 5 yrs | 1428 (33,6) | 1019 (32,3) | 348 (37,5) | 61 (36,5) | |
| 6 – 10 yrs | 1465 (34,5) | 1077 (34,2) | 332 (35,8) | 56 (33,5) | |
| > 10 yrs | 1353 (31,9) | 1056 (33,5) | 247 (26,6) | 50 (29,9) | |
| Mean ± SD | 8,81 ± 4,2 | 9.0 ± 4,3 | 8,3 ± 4,0 | 8,6 ± 4,3 | **P< 0,0001** |
| Median (range) | 8 (0-26) | 8 (0-26) | 8 (0-24) | 8 (1-26) | |
| **MMSE score** | | | | | **P= 0,037** |
| ≥ 24, N (%) | 3400 (80,1) | 2551 (80,9) | 724 (78,1) | 125 (74,9) | |
| < 24, N (%) | 846 (19.9) | 601 (19,1) | 203 (21,9) | 42 (25,1) | |
| Mean ± SD | 26,05 ± 3,71 | 26,2 ± 3,6 | 25,8 ± 3,75 | 25,3 ± 4,5 | **P = 0,001** |
| Median (range) | 27 (3,3-30) | 27 (3,3-30) | 27 (5,6-30) | 27 (8-30) | |

# Tab. 2: Crude OR and 95% CI of scoring below 24 at the MMSE according to the ACB score

| | Crude OR | 95 % CI |
|---|---|---|
| **ACB score 0** | 1 | |
| **ACB score 1** | 1,19 | 1,00- 1,42 |
| **ACB score 2** | 1,43 | 1,00- 2,05 |

# Tab. 3 OR and 95% CI of scoring below 24 at the MMSE in relation to the ACB score adjusted for demographic variables

| | OR | 95 % CI |
|---|---|---|
| **Age ≤ 70 yrs** | 1 | |
| **71- 80 yrs** | | 1,24- 2,13 |
| **> 80 yrs** | | 2,61- 4,4 |
| **Gender Male** | 1 | |
| **Female** | 0,91 | 0,77- 1,08 |
| **Education > 10 yrs** | 1 | |
| **6-10 yrs** | | 1,63- 2,49 |
| **< 5 yrs** | | 2,02- 3,08 |
| **ACB score 0** | 1 | |
| **1** | 1,01 | 0,84- 1,23 |
| **2** | 1,3 | 0,89- 1,89 |

## Tab. 4 OR and 95% CI of scoring below 24 at the MMSE in relation to baseline ACB Score, stratified by age.

| | <71 yrs | | 71-80 yrs | | >80 yrs | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| **ACB score 0** | 1 | | 1 | | 1 | |
| **1** | 1,33 | 0,72- 2,47 | | 0,87- 1,57 | 0,95 | 0,74- 1,22 |
| **2** | 1,02 | 0,23- 4,47 | | 0,71- 2,35 | 1,32 | 0,80- 2,18 |

## Tab. 5 OR and 95% CI of scoring below 24 at the MMSE in relation to baseline ACB Score, stratified by education.

| | <5 yrs | | 5-10 yrs | | >10 yrs | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| **ACB score 0** | 1 | | 1 | | 1 | |
| **1** | 1,15 | 0,88- 1,5 | 0,96 | 0,71- 1,3 | | 0,97- 2,18 |
| **2** | 1,12 | 0,63- 1,99 | 1,62 | 0,90- 2,92 | | 0,74- 3,54 |

# Discussion

- About **one quarter** of elderly subjects with first cognitive complain received in the primary care setting at least one drug with anticholinergic action.
- The association between the use of anticholinergic drugs and the impairment in cognition, measured with the MMSE, adjusted for demographic variables, although not statistically significant might be **clinically relevant** from a public health standpoint.

# Strenghts of the study

- The **large sample size** allows to make inferences that reflect the real world clinical practice.
- Moreover, the present study deals with a very **relevant clinical point** and might contribute to understand the risk factors associated with cognitive decline.
- The **primary care setting** is relevant for taking decision in a **public health perspective**.

# Limitations of the study

- The **observational nature**: the present study can't prove neither a causal link nor the direction of the association between the use of anticholinergic drugs and the impairment in cognition.
- Some information about some variables that could influence the cognitive performance of the patients are missing, including the **duration of anticholinergic treatment.**
- **Indication bias**: when a treatment serves as a marker for a clinical characteristic or medical condition taht triggers the use of the treatment and that, at the same time, increases the risk of the outcome under the study.

# Future perspective

- In the context of the cross- sectional study it will be possible to investigate the role of the ACB score in the **subitems of the MMSE**. Moreover, in those subjects sent to the MCs, we will correlate the ACB score with the **neuropsychological assessment**.

- Since this study in a part of a 3-year population-based prospective cohort study, we will evaluate the association between the ACB score and **the diagnosis of dementia made by specialists**.

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| | |
|---|---|
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# Thanks!

**http://intranet.asl.milano.it/_asl/Alzheimer/Default.htm**