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# ANTICHOLINERGIC EXPOSURE IN A COHORT OF ADULTS AGED 80 YEARS AND OVER

## *ASSOCIATIONS OF THE MARANTE SCALE WITH MORTALITY AND HOSPITALISATION*

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Competing interest

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*Abstract:* Anticholinergics are frequently prescribed for older adults and can lead to adverse drug events. The novel MARANTE (Muscarinic Acetylcholinergic Receptor ANTagonist Exposure) scale measures the anticholinergic exposure by incorporating potency and dosages of each medication into its calculations.

The aims were to assess prevalence and intensity of the anticholinergic exposure in a longitudinal cohort study of community-dwelling patients aged 80 years and over (n=503) and to study the impact on mortality and hospitalisation.

Chronic medication use at baseline (November 2008 - September 2009) was entered and codified with the Anatomical Therapeutic Chemical classification. Time-to-event analysis until first hospitalisation or death was performed at 18 months after inclusion, using Kaplan-Meier curves. Cox regression was performed to control for covariates.

Mean age was 84 years (range 80 – 102), and mean number of medications was 5 (range 0 – 16). Prevalence of anticholinergic use was 31.8%, with 9% taking ≥2 anticholinergics (range 0 – 4). Main indications for anticholinergics were depression, pain and gastric dysfunction. Female gender, the level of multimorbidity and the number of medications were associated with anticholinergic use.

Mortality and hospitalisation rate were 8.9%, and 31.0% respectively. After adjustment for the level of multimorbidity and medication intake, multivariable analysis showed increased risks of mortality (HR 2.3, 95%CI 1.07 – 4.78) and hospitalisation (HR 1.7; 95%CI 1.13 – 2.59) in those with high anticholinergic exposure.
The longitudinal study among Belgian community-dwelling oldest old demonstrated great anticholinergic exposure, which was associated with increased risk of mortality and hospitalization after 18 months.

## KEY POINTS

- The novel MARANTE scale incorporates potency and dosages, resulting in a robust method to estimate exposure to anticholinergics.
- The MARANTE scale clearly indicates strong associations between a high anticholinergic exposure and adverse outcomes in the community-dwelling older old.
- In multivariable analysis, a high anticholinergic exposure was associated with a 2.2-fold increased risk of mortality and a 71% increased risk of hospitalisation during an observation period of 18 months.

Medications with anticholinergic properties (anticholinergics) block the effect of acetylcholine on the muscarinic and nicotinergic receptors in central or peripheral organ systems, inhibiting the acetylcholine-mediated response [1–6]. Anticholinergics are widely prescribed in older patients [5–7] for several indications (including depression, psychosis, allergy, ...). Often prescribers do not perceive the prescribed drug as an anticholinergic [8].
On top of the higher level of comorbidities and the higher overall medication intake, older persons become more sensitive to the side-effects of anticholinergics due to a decreased elimination of medications, as well as an increased permeability of the blood-brain barrier [7,9–

11]. Inhibition of acetylcholinergic mediated muscle contraction can lead to peripheral side effects, which include blurred vision, urine retention or constipation. Competitive binding to muscarinic brain receptors can lead to central nervous symptoms, which include dizziness, hallucinations or confusion. These side effects can again in the long term lead to the appearance of delirium [12], impaired cognitive function[13], an increased number of falls[14] and hospital readmission risk [15]. Usage of anticholinergics has been linked to an increased risk of mortality and hospitalisation [16,17].

Only scoring the anticholinergic potency of medications to quantify the anticholinergic exposure is deemed too simplistic as it should also incorporate the dose-relationship [18]. In the past decades, several Anticholinergic Risk Scales (ARS) have been created to measure the anticholinergic burden in older patients. All these tools list medications with anticholinergic properties and quantify the intrinsic burden of each medication[19–25], but there is a significant variation on included drugs[26]. Dosage is only taken into account in two of them. The ARS by Carnahan *et al*. uses the maximal effective dosage, and it does not take dosage adjustments for older persons into account [19]. The Drug Burden Index (DBI) calculates the anticholinergic burden using only the minimal effective value of medications. However, the anticholinergic nature of the medications listed in the DBI is unclear[5]; the DBI does not incorporate the anticholinergic potency of medications, and finally the minimal effective value of medications was determined for a younger population.

Results from studies using one dosage reference point did not validate whether a higher anticholinergic exposure is related to mortality or hospitalisation, neither in the short nor the long term [14,27–29]. Therefore, this study aimed (1) to determine accurately the point-prevalence and the intensity of the anticholinergic exposure using the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure through the MARANTE scale in a prospective cohort of oldest old primary care patients (aged 80 years and over), and (2) to investigate associations with mortality and first hospitalisation during an observation period of 18 months.

# METHODS

## SAMPLE

We used the Belfrail-Med cohort [30,31] of 503 Belgian community-dwelling primary care patients aged 80 years and over. All subjects were recruited by their own general practitioner between November 2008 and September 2009. Exclusion criteria were known dementia and being treated in palliative care.

## DATA COLLECTION

Baseline data included personal, clinical, functional and medication data and was collected by trained investigators and general practitioners (GPs). The trained investigators conducted structured questionnaires and standardised tests to collect personal (age, gender, life situation, …) and functional data (physical activity, activities of daily living and cognitive impairment). GPs performed clinical examinations and used their medical records to collect medication information and clinical data (current and past clinical problems in order to assess the level of multimorbidity). For a full background on the data collection and construction of the level of multimorbidity (Cumulative Illness Rating Scale, CIRS), see previous publications [32,33].

The GPs recorded all chronic medications at baseline. Chronic medications were defined as entries on the medication list without a stop date. All chronic medications with systemic effect were codified into the Anatomical Therapeutic Chemical classification (WHO ATC/DDD 2013) [34] based on the official register of medications on the Belgian market[1].

## CLINICAL AND FUNCTIONAL DATA HANDLING

For a full background on the clinical and functional data handling, we refer to the original Belfrail-Med article [30,31].

To measure the level of multimorbidity, the Cumulative Illness Rating Scale (CIRS) was used [35]. The CIRS measures the chronic medical illness burden while taking into consideration the

[1] Source: https://www.ehealth.fgov.be

severity of chronic diseases [36]. For the construction of the CIRS, all current and past medical problems were used. Out of 14 body systems, every body system affected with severe disease was counted, to a possible range of 14 [33,36].

To measure the physical activity, the LASA Physical Activity Questionnaire (LAPAQ) was used [37]. For our calculations, we divided the raw LAPAQ scores (range 0 - ∞) into quartiles to identify the lowest scoring quartile as those with the lowest physical activity.

Activities of Daily Living (ADL) were derived from the KATZ scale, which measures the care dependency in six domains: bathing, clothing, toileting, transferring, continence and feeding [38]. For our calculations, we divided the raw KATZ ADL scores (range 6 – 30) to identify those most care dependent (scoring 13 and more).

To identify cognitive impairment, we relied on the Mini-Mental State Examination (MMSE) [39]. A cut-off adapted to the age and level of education of the respondents was used to identify cognitive impairment [40].

## ASSESSING ANTICHOLINERGIC EXPOSURE

To evaluate anticholinergic exposure, we used the MARANTE scale, based on the systematic review by Durán *et al.* (2013)[41] and a methodological study by Klamer & Wauters [42]. Duran listed 100 active substances with anticholinergic properties originating from 7 anticholinergic risk scales (ARSs), and categorised them according to their anticholinergic potency (low or high) [41]. In Klamer & Wauters' study, for 41 active substances (increasing to 69 when counting variations of routes of administration, pharmaceutical forms, or combination products), 3 dosage reference values were identified. All reference values were based on information from authorative sources and then validated and completed by an expert panel.

## CALCULATING THE ANTICHOLINERGIC EXPOSURE

The MARANTE scale is the summation of all anticholinergic loads in a patient's medication list. The anticholinergic load is calculated by multiplying the values of potency and daily dosage of each medication. Patients not taking anticholinergics receive a score of 0. A complete overview of the calculation of the score on the MARANTE scale is given in Box 1.

### *POTENCY*

For potency, we used the distinction between a low and high anticholinergic potency as suggested in Duran's list and the Klamer & Wauters study [42], with a value of 1 for low potency, and 2 for high potency anticholinergics.

### *DOSAGE*

For dosage, we determined the daily dosage per anticholinergic from the posology instructions in the medication list. The daily dosage equals the sum quantities of all doses given to a patient of a specific medication during the course of 1 day.

This daily dosage is compared to the reference values (set in Kramer & Wauters *et al*., 2016), and based on the pharmacological concepts: minimal geriatric effective value (GMinEV), maintenance geriatric dosage (GMainD), and maximum geriatric effective value (GMaxEV). These reference points permit to accord values for very low, low, high and very high daily dosage ranges.

- A dosage higher than 0 mg, and below GMinEV received a dosage score of 0.5.
- A dosage equal/higher than GMinEV and below the maintenance geriatric dosage (GMainD) was scored 1.
- Equal/above GMainD and below the maximal effective geriatric dosing (GMaxEV) was scored 1.5,
- All dosages equal/above GMaxEV received a dosage score 2.

## FOLLOW-UP DATA

Follow-up data included data on mortality (date and cause of death) and hospitalisation (date of the first hospitalisation) during an observation period of 18 months. A hospitalisation was defined as an unplanned hospital stay lasting longer than one day. Index date was the date of baseline assessment.

## STATISTICAL ANALYSIS

All statistical analyses were done using SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). For all variables, there was less than 5% missing data [30].

Descriptive statistics include means, and standard deviations or range for normally distributed data, and medians with interquartile range for skewed data. Categorical data were expressed using numbers and percentages.

After calculation of all the scores of the MARANTE scale, the results were categorized in low and high anticholinergic exposure, based on the median of the distribution (lower than and above the median). For each patient, we also calculated separately the sum of the values for potency, and the sum of values for the dosage, to explore the impact of the two elements of the MARANTE scale.

Time-to-event analysis was estimated using the Kaplan-Meier method, with the log-rank test verifying differences in time-to-event between groups (no *versus* low, low *versus* high and no *versus* high anticholinergic exposure). A follow-up period of 18 months after inclusion was used to observe direct associations of mortality and unplanned hospitalization with the baseline anticholinergic exposure of patients. Death or unplanned first hospitalization were considered as events. For hospitalization, additional censoring was applied for patients who died. All relations between anticholinergic exposure and outcomes were based on the baseline medication intake without proof of a continuous (chronic) anticholinergic intake throughout the study period.

Univariable and multivariable analyses were done to calculate Hazard Ratios for the associations with mortality and hospitalisation. The MARANTE scale was used in univariable and multivariable analyses as a continuous variable but also as categorical variable. Categories dividing no, low and high exposure were formed based on the distribution of the scores on the MARANTE scale. Categorical analysis was performed to observe trends in associations between anticholinergic exposure and outcomes. In the multivariable analysis, we corrected the associations with outcomes, for the number of medications taken at baseline and with the level of multimorbidity. The level of multimorbidity (CIRS, as a continuous variable) was chosen because of the dominating association over other patient characteristics (for more background details, see the original Belfrail-Med paper [43]).

### ETHICAL APPROVAL

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics committee of Ghent University Hospital (B670201421408, on 26/06/2014). All participants provided informed consent.

## RESULTS

### DESCRIPTION OF THE POPULATION

The mean age of patients in the Belfrail-Med cohort (n=503) was 84.4 years (range 80 - 102). The majority was female (61%) and with a low level of education (≤ 8 years, 69%).

The median level of multimorbidity, expressed by the CIRS, was 4 (range 1 -9). The most common clinical problems were hypertension (70.4%), osteoarthritis (57.1%), hyperlipidaemia (44.1%) and heart failure (38.4%)

The mean number of chronic medications prescribed was 5.4 (range 0 – 16). Prescribing of 5 or more medications was present in 57.7%, and in 0.8% there was no chronic medication use.

Predominant main anatomical medication classes (1st ATC level) were cardiovascular medications (in 86.3% of the population), followed by blood regulating medications (56.1%), and nervous system medications (54.5%). The most prescribed therapeutic subgroup (2nd ATC level) was antithrombotic medications (54.5%).

All personal and clinical characteristics, as well as the description of the general medication use of the study population are given in Table 1.

### DESCRIPTION OF THE ANTICHOLINERGIC USE

In this population of community-dwelling oldest old, 68.2% had no medications with anticholinergic properties prescribed on a chronic basis; 23% were taking 1 anticholinergic; 7.0% 2, 1.2% 3 and 0.6% were taking 4 anticholinergics.

In total, 217 prescriptions of medication with anticholinergic properties were identified. Most often these anticholinergic prescriptions were of low potency (80.0%). The dosages in which

anticholinergics were prescribed were rarely considered too low (1.8% below GMinEV), yet often high (51.5% above GMainD) or very high (17.1%, above GMaxEV).

Medications with anticholinergic effects (n=217) were predominantly ATC N (nervous system medications) for the treatment of depression (35.0%, predominantly escitalopram, trazodone and citalopram) or for pain (18.4%, predominantly tramadol). Other predominantly prescribed medications in ATC A (alimentary medications) were for the treatment of gastrointestinal disorders/peptic ulcers (20.7%; predominantly ranitidine and domperidon). Anticholinergics in ATC R (respiratory agents) were for treatment of asthma (8.8%) or ATC G (genito-urinary medications) for the treatment of urinary problems (5.5%).

## DESCRIPTION OF THE ANTICHOLINERGIC EXPOSURE

The scores on the MARANTE Scale ranged between 0 – 7.

Based on the distribution of the MARANTE, two equal groups were created. One low-exposure group (MARANTE 0.5 – 1.5, 16.1%) and a high-exposure group (MARANTE ≥ 2, 15.7%). As a consequence, to be categorised into the high-exposure group, it would sufficient to take one high potency anticholinergic at a low dose (above GMinEV) or a low potency at a very high dose (above GMaxEV). To be categorised into the low-exposure group, a high potency could only be taken at the lowest dose (below GMinEV) or a low potency at a dose lower than the GMaxEV, or the combinations of maximum three low potency anticholinergics at the lowest doses.

The description of the anticholinergic use is given in Table 2.

## PATIENT CHARACTERISTICS ASSOCIATED WITH ANTICHOLINERGIC USE

All personal, clinical, functional, and medication characteristics associated with the use of anticholinergics are presented in Table 3.

Personal factors associated with anticholinergic use were female gender (OR 1.55, 95% CI 1.04 – 2.30) and low education (OR 1.80, 95% CI 1.16 – 2.79). Age was not associated with anticholinergic use in this cohort of oldest old patients.

Clinical characteristics associated with anticholinergic use included the level of multimorbidity (OR 1.28, 95% CI 1.14 – 1.44), predominantly depression (OR 5.22, 95%CI 2.99 – 9.12).
For the functional characteristics, physical inactivity (OR 2.05, 95% CI 1.34 – 3.12), but neither cognitive impairment nor care dependency showed associations with anticholinergic use.
Both the level of medication use (expressed as a continuous variable) and the dichotomous variable of polypharmacy were strongly associated with anticholinergic use.

## SURVIVAL ANALYSIS OF ANTICHOLINERGIC EXPOSURE ON MORTALITY AND HOSPITALISATION

The unadjusted survival analyses of different categories of anticholinergic exposure on mortality and first hospitalisation are given in Graph 1.
The mortality rate after 18 months was 8.9% (n=45). Most common causes of death were cardiovascular and/or cerebrovascular related events (48.9% of deaths), cancer (20.0%), respiratory-related events (13.3%) or general deterioration (6.7%). The survival rate was lower among those who had high anticholinergic exposure, as compared to those without. There was only a significant difference in survival percentage between those with no (93.3%) *versus* those with high (85.0%, p=0.001) anticholinergic exposure.
The Time-to-event analysis showed that the probabilities of having a hospitalisation (31%, n=156) varied among the categories of anticholinergic exposures. Those with high anticholinergic potency (45.7%) had a significantly lower hospitalisation rate than those with no (74.6%, p<0.001) and low anticholinergic exposure (68.2%, p=0.003). There was no difference in survival rates (p=0.626) in those with low and no anticholinergic exposure.

## UNIVARIABLE ANALYSIS FOR THE ASSOCIATION OF THE MARANTE SCALE WITH MORTALITY AND HOSPITALISATION

All univariable associations with mortality and first hospitalisation are given in Table 4.
For mortality and for hospitalisation, the continuous variables for the number of anticholinergics, the potency score, the dosage score and the score on the MARANTE Sale, showed all significant increased risks. The Hazard Ratio for the MARANTE scale had a more

narrow confidence interval than the potency and dosage scores for both outcomes, potentially indicating a higher precision. For the low anticholinergic exposure category, no significantly increased risks were observed.

Age, the level of multimorbidity (CIRS) and the number of medications were also associated with mortality and hospitalisation.

Those with a high anticholinergic exposure (MARANTE scale ≥2) had a 2.8-fold increased risk of mortality (HR 2.77, 95% CI 1.43 – 5.38) and a 2.4-fold increased risk of hospitalisation (HR 2.36, 95% CI 1.63 – 3.42) compared to those with no anticholinergic exposure.

Multivariable associations with mortality and first hospitalisation are given in Table 5. Two models are presented - the first was adjusted for the number of medications and the second for both the number of medications and for the level of multimorbidity.

Associations between the number of anticholinergics, the potency score and dosage score disappeared in the multivariable analysis.

The analysis based on the scores on the MARANTE scale did yield statistically significant and clinically relevant results. For both outcomes, the Hazard Ratio for the MARANTE scale (continuous variable) had more narrow confidence intervals than the potency and dosage scores, potentially indicating higher precision.

In the multivariable analysis model, the anticholinergic exposure quantified by the MARANTE scale was categorised and adjusted for confounding variables. Only-significant associations were found for those with high anticholinergic exposure for both mortality (HR 2.20, 95% CI 1.03 – 4.67) and for first unplanned hospitalisation (HR 1.71, 95% CI 1.13 – 2.59).

# DISCUSSION

## MAIN FINDINGS

In this longitudinal study, we applied for the first time a new anticholinergic scale based on both potency and the whole dosage spectrum. Our main finding is that the MARANTE scale is a robust and potent approximation for quantifying anticholinergic exposure.

We were able to show that a third of this community-dwelling cohort over oldest old (aged 80 years and older) takes chronically at least one medication with anticholinergic properties. Anticholinergics with low potency (80% of all anticholinergics) were most consumed, yet dosing was considered often high (52%) or very high (17%) in this population.

Based on the median score on the MARANTE scale in subset of patients with anticholinergic exposure, equal groups were created. Those with a high anticholinergic exposure (a score ≥ 2 on the MARANTE scale) showed increased risks of both mortality and hospitalisation in multivariable analysis, controlling for the number of medications and the level of multimorbidity. These patients showed a 2.2-fold increased risk of mortality, and a 71% increased risk of being hospitalised during an observation period of 18 months.

## STRENGTHS AND LIMITATIONS

We explored the point-prevalence and intensity of the anticholinergic exposure at baseline in a cohort of community-dwelling oldest old with a new measurement instrument, taking into account potency and dosage. We studied the intensity of the baseline anticholinergic exposure, by looking at associations with mortality and first unplanned hospitalization using a prospective cohort during an observation period of 18 months, The observational nature of this study does not permit to ascertain causal relations of the anticholinergic exposure with outcomes. Confounding by indication is possible as anticholinergics are used in patients with multiple diseases, all possibly associated with the outcomes.

In multivariable analysis, taking into account multimorbidity and polypharmacy, simple measures of anticholinergic exposure (number of anticholinergics, sum of values for potency,

sum of values for dosage) failed to observe significant results. Only the application of the MARANTE Scale, and the subsequent categorisation in two groups of low and high exposure revealed that high anticholinergic exposure is associated with mortality and hospitalisation.
Only the chronic medication use was analysed (no *if-needed* or over-the-counter medications), potentially underestimating the anticholinergic exposure. All associations with mortality or first hospitalisation were based on the baseline chronic medication intake, without control for a continuous chronic anticholinergic intake during the observation period.
It should also be remembered that this cohort was limited to community-dwelling active and cognitively fit oldest old, limiting the transferability and interpretation into other populations.
In this study, only associations with mortality and hospitalisation were analysed. The data collection of the original Belfrail cohort was not intended to look at the symptomatic adverse events of medications (e.g. sedation). All participants were randomly and consecutively selected by their GPs; thus, some degree of prevalent user bias cannot be excluded.
The MARANTE scale is built on the premise of a pure additive effect of different anticholinergic loads and does not consider possible synergistic or antagonistic effects of medications at the receptor level.

## IN RELATION TO OTHER FINDINGS

With advancing age, the consumption of medications will rise as well, and consequently the intake of anticholinergics will rise [11]. Other studies estimate that up to 51% of the community-dwelling population take medications with anticholinergic properties [44], yet interpretation of this prevalence should be done with caution. Depending on the method used for classifying anticholinergics, the prevalence of anticholinergic use in just one population of older community-dwelling men could range between 13 – 39% [45].
Our findings are in concordance with other studies, searching for associations between patient characteristics and the use of anticholinergics. The association of anticholinergic use with female gender, age, depression, the number of medications, multimorbidity and with the number of medications have been observed before [46–48]. In this study, the association with

cognitive impairment was absent [7,22], since older adults without dementia were included in the Belfrail-med cohort.

Anticholinergics have been considered as potentially inappropriate [49,50] and are widely regarded as to be used with caution in older persons. However, the definition of medications with anticholinergic properties varies significantly, leading to a multiplicity of lists and explicit criteria, making a direct comparison difficult to perform. In addition, given different samples used, and different cut-offs for what high anticholinergic exposure is [51], associations with mortality and hospitalisation remain inconclusive or even contradictory.

Previous publications did not find consistent associations of anticholinergic exposure with mortality or hospitalisation[14,17,18,27,46,29,52,53]. Limiting the results to the oldest old (aged 80 years and older), one longitudinal study reported significant associations with mortality [53], while others did not [14,17,27]. For hospitalisation, in one publication, a significant, yet limited association was found in the oldest old [29].

Our findings suggest an increase in mortality and first unplanned hospitalisation with high anticholinergic exposure. Although associations were absent for a low anticholinergic exposure, the risks were still increased for both outcomes. The clinical relevance of a low anticholinergic exposure must not be disregarded. A low anticholinergic exposure might be associated with other clinical problems (e.g. more anticholinergic side-effects).

## IMPLICATIONS FOR PRACTICE

Medication prescribers will need education and assistance to appreciate the importance of these 'invisible' anticholinergic medicines (and the patient contexts in which they are prescribed) and to incorporate calculations of individual patient anticholinergic exposure into their clinical decision-making. This has the potential to reduce patients' anticholinergic exposure and adverse drug events.

Medications with anticholinergic properties are not always known to prescribers [8], nor are anticholinergic side effects recognised. The array of tools and methods available, each using different medications, can lead to confusion in knowing the true anticholinergic properties of

medications. The MARANTE scale can aid medication prescribers to recognise those patients with high anticholinergic exposure and to monitor these patients more systematically for their experienced side-effects.

Past and recent interest in anticholinergics in older adults, understresses the importance of a consensus on a unified list of medications with anticholinergic properties, with agreements on their potency and dosages. We therefore invite other researchers to an open discussion at http://marante.ramit.be/marante/.

A computerised application of the MARANTE scale in older adults can be used to implement particular explicit criteria of inappropriate prescribing in automated systems of decision support and quality assurance, but it should not be used as a substitute for the clinical assessment of the pharmacological therapy of an individual patient.

## IMPLICATIONS FOR RESEARCH

This cohort consisted of relatively healthy and active older adults (aged 80 years and older). It would also be interesting to examine the effects of a high anticholinergic exposure in older adults, aged 65 years and older. Also the associations of a higher anticholinergic exposure with outcomes are to be studied in more frail patients in nursing homes, where there are more patients with dementia, who are more susceptible to the anticholinergic effects [2,6]. Older adults in nursing homes have a higher medication intake, predominantly more psychotropic medications and possibly a higher anticholinergic exposure [54,55].

Finally, it is important to relate the anticholinergic exposure to the anticholinergic burden, e.g. the direct burden perceived by patients. Other studies reported associations of anticholinergic exposure with lower quality of life [56], possibly due to a higher prevalence of common anticholinergic adverse effects (sedation, hallucinations, dry mouth or constipation). Therefore, in a following study, we will investigate associations of anticholinergic exposure (quantified by the MARANTE scale) with the anticholinergic burden.

## CONCLUSION

In a cohort of community-dwelling oldest old (aged 80 years and over), a high prevalence of anticholinergic use was observed, predominantly in high and very high dosages. The novel MARANTE scale provided a robust estimation of the anticholinergic exposure but further validation is still needed. Those with high anticholinergic exposure showed increased risks of mortality and hospitalisation.

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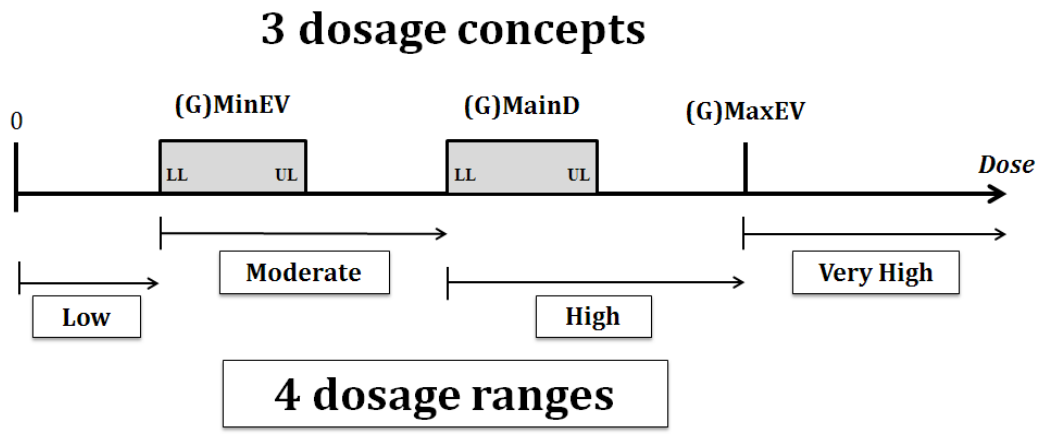
# TABLES

Box 1: Schematic overview of the construction of the MARANTE Scale

1. Anticholinergic dosage terms and value scoring (per medication)




2. Anticholinergic load for one medication

potency × dosage score = (p × d)

3. Value scoring of the MARANTE scale

Sum of all anticholinergic loads for n medications

$\mathbf{MARANTE} = \sum_{1\rightarrow n}^{n}(\boldsymbol{p_n} \times \boldsymbol{d_n})$

Box legend: LL: Lower limit UL: Upper Limit. GMinV: Minimal geriatric effective value. GMainD: Maintenance geriatric dosage. GMaxEV: Maximal effective geriatric dosing.

Table 1: Personal, clinical and functional characteristics, and the general medication use of the study population (n=503).

| | | |
|---|---|---|
| Personal | | % |
| | Mean age in years (range) | 84.4 (80 - 102) |
| | Gender (% female) | 61.2 |
| | Low education (≤ 8 years) | 69.2 |
| | Living alone | 43.3 |
| Clinical[1] | | |
| | Median level of Multimorbidity (range) | 4 (IQR 3 - 5) |
| | Hypertension | 70.4 |
| | Osteoarthritis | 57.1 |
| | Hyperlipidaemia | 44.1 |
| | Heart Failure (NYHA[2]> 0) | 38.4 |
| | Obesity (BMI > 30kg/m²) | 27.9 |
| | Osteoporosis | 20.9 |
| Functional | | Median (IQR*) |
| | Activities of daily living, ADL | 6 (6 - 8) |
| | Physical activity, LAPAQ | 70 (30 – 102) |
| | Mental status, MMSE | 28 (26 – 29) |
| Medication use | | |
| | Mean number of chronic medications | 5.4 (range 0 – 16) |
| | Patients with polypharmacy (5 or more) | 57.7 |
| Most prevalent prescribed medication subclasses (>15%) | | |
| | Antithrombotic agents | 54.5 |
| | Beta blocking agents | 41.9 |
| | Medications acting on RAAS | 41.9 |
| | Benzodiazepines and Z-drugs | 35.6 |
| | Lipid modifying medications | 33.2 |
| | Diuretics | 32.0 |
| | Drugs for acid related disorders | 24.5 |
| | Calcium channel blockers | 24.3 |
| | Cardiac therapy medications | 20.7 |
| | Mineral supplements | 16.7 |
| | Analgesics | 16.5 |
| | Antidepressants | 16.1 |
| | Medications used in diabetes | 15.9 |

[1]Clinical problems with prevalence above 20% are listed.
[2]New York Heart Association (NYHA) functional classification of heart failure
*IQR: Inter quartile range

Table 2: Description of anticholinergic use in the study population (n=503)

| General description | | n=503 | % |
|---|---|---|---|
| Anticholinergics use | | | 31.8 % |
| Range of number of Anticholinergics | | | 0 – 4 |
| Range of potency scores | | | 0 – 5 |
| Range of dosage scores | | | 0 – 6 |
| Range of scores on the MARANTE scale | | | 0 – 7 |
| Details of anticholinergics | | n=217 | % |
| Potency | Low | | 80.0 |
| | High | | 20.0 |
| Dosage | Below GMinEV (very low) | | 1.8 |
| | Above GMinEV (low) | | 30.0 |
| | Above GMainD (high) | | 51.5 |
| | Above GMaxEV (very high) | | 17.1 |
| Most prevalent anticholinergics (>2%) | | n=217 | |
| A02BA02 | Ranitidin | | 14.7 |
| N02AX02 | Tramadol | | 10.1 |
| N06AB10 | Escitalopram | | 8.8 |
| R03AL01 | Ipratropium bromide* (+ Fenoterol) | | 7.4 |
| N06AX05 | Trazodone | | 7.4 |
| A03AF03 | Domperidone | | 5.5 |
| N02AX52 | Tramadol (combination products) | | 5.5 |
| N06AB04 | Citalopram | | 4.6 |
| G04BD04 | Oxybutinin* | | 4.1 |
| N06AA09 | Amitriptyline* | | 3.7 |
| N06AX11 | Mirtazapine | | 3.7 |
| N06AB05 | Paroxetine | | 3.7 |
| Anticholinergic Exposure (MARANTE) categories | | n=503 | % |
| No | 0 | | 68.2 |
| Low | 0,5 – 1.5 | | 16.1 |
| High | ≥ 2 | | 15.7 |

Medications market with an * are high potency anticholinergics

Table 3: Univariable analysis of personal, clinical, functional characteristics and medication use of the Belfrail-Med cohort (n=503) in relation to anticholinergic use.

| | Anticholinergic use? Yes n=160 | No n=343 | | Univariable odds ratio (95% C.I.) |
|---|---|---|---|---|
| Personal | % | % | p-value | |
| *Mean age* (in years) | 84.5 | 84.4 | .718 | |
| Female gender | 68.1 | 58.0 | .030 | 1.55 (1.04 – 2.30) |
| Living alone | 44.4 | 42.9 | .749 | |
| Low education (≤8 years) | 78.0 | 66.3 | .008 | 1.80 (1.16 – 2.79) |
| Clinical | | | | |
| Mean comorbidity, CIRS | 4.2 | 3.6 | <.001 | 1.28 (1.14 – 1.44) |
| Hypertension | 65.0 | 73.1 | .064 | |
| Osteoarthritis | 69.6 | 52.8 | <.001 | 2.05 (1.37 – 3.06) |
| Hyperlipidaemia | 46.8 | 44.6 | .639 | |
| Heart Failure | 40.6 | 37.3 | .477 | |
| Osteoporosis | 32.4 | 18.9 | .001 | 2.39 (1.52 – 3.75) |
| Obesity | 30.4 | 27.8 | .548 | |
| Diabetes | 18.9 | 19.1 | .959 | |
| Post myocardial infarction, post stroke | 20.6 | 17.9 | .472 | |
| COPD/Asthma | 19.4 | 12.5 | .045 | 1.68 (1.01 – 2.83) |
| Depression | 26.6 | 6.5 | <.001 | 5.22 (2.99 – 9.12) |
| Chronic renal failure | 16.8 | 8.9 | .011 | 2.06 (1.17 – 3.61 |
| Functional | | | | |
| Most care dependent (ADL) [1] | 6.3 | 10.7 | .120 | |
| Most physical inactive (LAPAQ) [2] | 34.8 | 20.6 | .001 | 2.05 (1.34 – 3.12) |
| Cognitive impairment (MMSE) [3] | 15.9 | 14.9 | .774 | |
| Medication related | | | | |
| Number of medications (0 – 16) | 7.2 | 4.6 | <.001 | 1.39 (1.29 – 1.51) |
| Polypharmacy users | 78.8 | 47.8 | <.001 | 4.05 (2.62 – 4.24) |

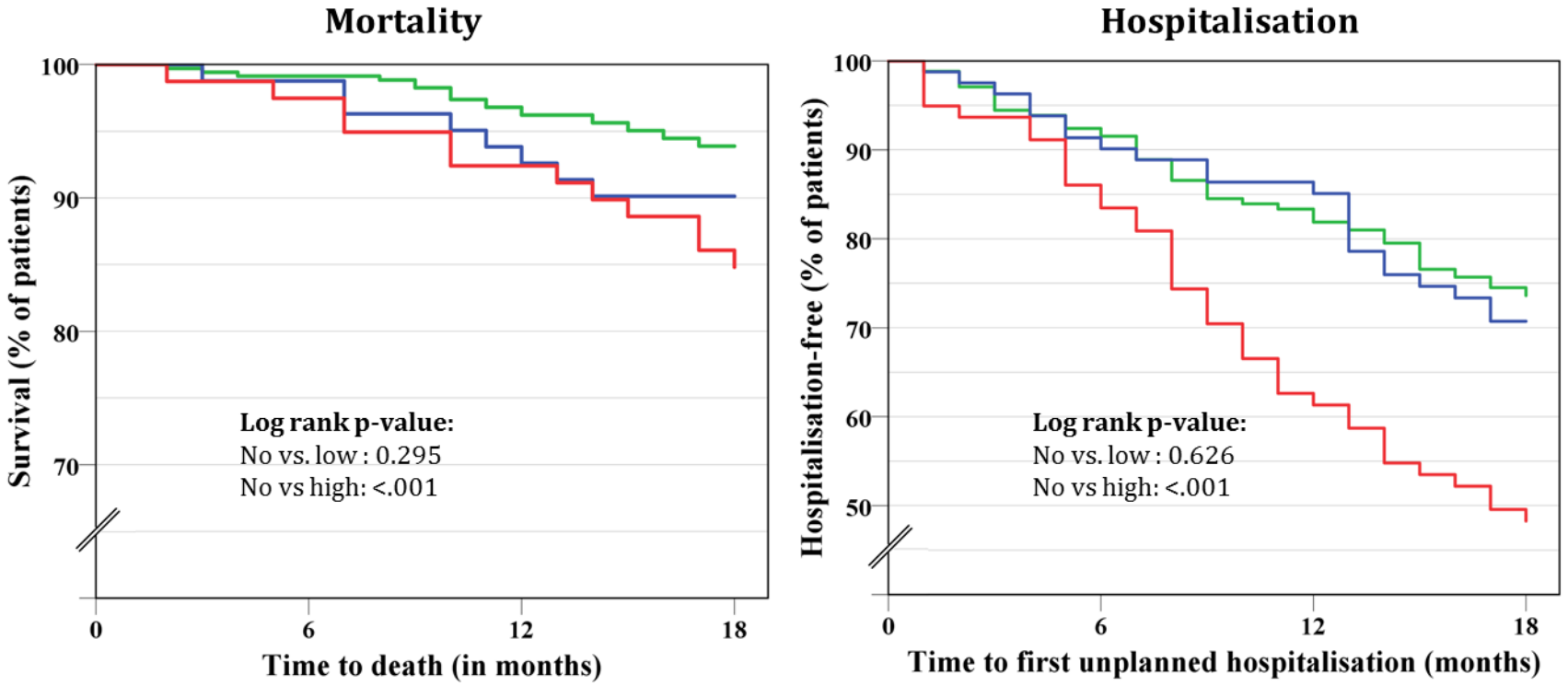
[1] Highest care dependency was defined as respondents scoring ≥ 13 (9.1%) on the KATZ ADL scale.
[2] Lowest physical active was defined as the quartile (25.2%) with the lowest raw score on the LAPAQ.
[3] Cognitive impairment was defined using the MMSE, adjusted for age and level of education.
**Only significant univariable odds ratios are shown.**

Table 4: Univariable analysis of the place of anticholinergic exposure and confounding variables in association with mortality and first hospitalisation

| ANTICHOLINERGIC EXPOSURE | | | MORTALITY | HOSPITALISATION |
|---|---|---|---|---|
| Continuous | Range | | HR (95% CI) | HR (95% CI) |
| Number of anticholinergics | 0 – 4 | | 1.40 (1.02 – 1.93) | 1.39 (1.17 – 1.67) |
| Potency score | 0 – 5 | | 1.33 (1.04 – 1,70) | 1.32 (1.15 – 1.52) |
| Dosage score | 0 – 6 | | 1.26 (1.01 – 1.58) | 1.29 (1.14 – 1.45) |
| MARANTE scale | 0 – 7 | | 1.22 (1.02 – 1.47) | 1.25 (1.13 – 1.38) |
| Categorical | Cut-off | N | | |
| Taking anticholinergics | | 160 | 2.13 (1.19 – 3.82) | 1.69 (1.23 – 2.33) |
| MARANTE scale | 0 | 343 | Ref | Ref |
| | Low (0.5 – 1.5) | 81 | 1.52 (0.68 – 3.39) | 1.14 (0.73 – 1.79) |
| | High (≥ 2) | 79 | 2.77 (1.43 – 5.38) | 2.36 (1.63 – 3.42) |
| CONFOUNDING VARIABLES | | | | |
| Continuous | Range | | | |
| Number of medications | 0 - 21 | | 1.12 (1.02 – 1.22) | 1.14 (1.08 – 1.20) |
| Age (years) | 80 - 102 | | 1.09 (1.01 – 1.16) | 1.04 (0.998 – 1.08) |
| Categorical | | | | |
| Female gender | | | 0.94 (.52 – 1.70) | 0.89 (0.65 – 1.22) |
| Low education (≤8 years) | | | 0.83 (.45 – 1.55) | 1.03 (0.73 – 1.45) |
| Living alone | | | 1.15 (.64 – 2.07) | 1.06 (0.77 – 1.46) |
| Multimorbidity[1] | | | 1.36 (1.15 – 1.59) | 1.25 (1.14 – 1.36) |
| Polypharmacy | | | 1.87 (0.98 – 3.56) | 1.69 (1.21 – 2.36) |

[1] Multimorbidity was expressed using the CIRS.

Graph 1: Survival analysis of groups of MARANTE scale (No, Low, and High anticholinergic exposure) for mortality and hospitalisation.




| | 0 | 6 | 12 | 18 | Legend | 0 | 6 | 12 | 18 |
|---|---|---|---|---|---|---|---|---|---|
| Number of Patients | 343 | 340 | 330 | 320 | 0 Green | 343 | 313 | 278 | 256 |
| | 81 | 80 | 75 | 73 | Low (0,5 – 1,5) Blue | 81 | 73 | 66 | 55 |
| | 79 | 77 | 72 | 67 | High (≥2) Red | 79 | 65 | 47 | 36 |

Table 5: Multivariable Cox regression analysis of mortality (8.9%) and hospitalisation (31%) in association with the anticholinergic exposure in a cohort of oldest old (n=503).

| | | | | Mortality | | Hospitalisation | |
|---|---|---|---|---|---|---|---|
| | Continuous | | Range | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| | | | | MODEL 1 | MODEL 2 | MODEL 1 | MODEL 2 |
| **APPROACH 1** | Number of anticholinergics | | 0 – 4 | 1.18 (0.80 – 1.74) | 1.14 (0.77 – 1.67) | 1.14 (0.92 – 1.41) | 1.12 (0.90 – 1.38) |
| | Potency score | | 0 – 5 | 1.17(0.86 – 1.58) | 1.14 (0.84 – 1.55) | 1.12 (0.95 – 1.33) | 1.12 (0.94 – 1.32) |
| | Dosage score | | 0 – 6 | 1.13(0.86 – 1.47) | 1.09(0.83 – 1.42) | 1.13 (0.98 – 1.31) | 1.11 (0.96 – 1.28) |
| | MARANTE | | 0 – 7 | 1.11 (0.89 – 1.39) | 1.09 (0.87 – 1.36) | 1.12 (0.99 – 1.26) | 1.10 (0.98 – 1.25) |
| | Categorical | Cut-offs | n | HR (95% CI) | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| **APPROACH 2** | MARANTE | 0 | 343 | Ref | Ref | Ref | Ref |
| | | Low (0.5 – 1.5) | 81 | 1.35 (0.59 – 3.08) | 1.31 (0.57 – 3.02) | 0.93 (0.59 – 1.49) | 0.93 (0.58 – 1.47) |
| | | High (≥ 2) | 79 | 2.26 (1.07 – 4.78) | 2.20 (1.03 – 4.67) | 1.75 (1.16 – 2.64) | 1.71 (1.13 – 2.59) |

Two approaches models were used. In the first one, associations of anticholinergic exposure with the continuous variable were analysed (e.g. the number of medications, and the continuous MARANTE score). In the second model, we performed categorical analysis to search for trends for a higher risk of mortality or hospitalisation with a higher anticholinergic exposure.
Two models were used, where model 1 was adjusted for the number of medications (0 – 16), and model 2 was additionally adjusted for the level of multimorbidity (0 – 9).