

The use of antidepressants in Belgian nursing homes: focus on indications and dosages in the PHEBE study.

Authors

Jolyce Bourgeois PharmD¹, Monique M. Elseviers MSc PhD^{1,2}, Luc Van Bortel MD PhD¹, Mirko Petrovic MD PhD^{1,3}, Robert H. Vander Stichele MD PhD¹

¹ Heymans Institute of Pharmacology, Ghent University, Ghent, Belgium

² Department of Nursing Science, University of Antwerp, Antwerp, Belgium

³ Service of Geriatrics, Ghent University Hospital, Ghent, Belgium

Running title: Indications and dosages of antidepressants.

Correspondence

Jolyce Bourgeois

Ghent University- Heymans institute

De Pintelaan 185 (1 block B)

9000 Ghent

Key words:

Antidepressants, older adults, nursing home, pharmacotherapy, drug utilisation, epidemiology

Word count main text: 4434

Acknowledgments

The authors have no conflict of interest relevant to the content of this study. No sources of funding were used to assist the completion of this original paper. Original data was obtained from the PHEBE study, which was sponsored by a research grant of the Belgian Health Care Knowledge Centre registered with the number 2005-17.

Description of the authors' roles:

Bourgeois J. formulated the research question, performed analyses and wrote the paper.

Elseviers M. formulated the research question, did the supervision of the statistical analyses and assisted with writing the paper.

Petrovic M. assisted with writing the paper and gave input from a clinical geriatric point of view.

Van Bortel L. assisted with writing the paper.

Vander Stichele R. formulated the research question, assisted with writing the paper and helped interpret the results.

TABLE OF CONTENTS

Authors	1
Running title:	1
Correspondence	1
Key words:	1
Acknowledgments	2
TABLE OF CONTENTS	3
ABSTRACT	5
Background & objectives:.....	5
Methods:	5
Results:	5
Conclusion:	6
ORIGINAL RESEARCH ARTICLE	7
<i>INTRODUCTION</i>	7
<i>METHODS</i>	9
Setting.....	9
Data collection.....	9
Classification of Antidepressants	9
Indication and dosages.....	10
Statistical analysis.....	11
<i>RESULTS</i>	12
Study population characteristics.	12
Antidepressant use at Resident level: prevalence and indications.....	12
Antidepressant use at Prescription level: prevalence and dose analysis.....	13
Characteristics associated with AD use.....	14

Characteristics associated with Antidepressant use for the indication ‘depression’ and ‘other’ indications.	14
Depression and dementia	14
<i>DISCUSSION</i>	15
STRENGTHS AND LIMITATIONS	15
DISCUSSION of the MAIN FINDINGS.....	16
Antidepressants for the indication ‘depression’	17
Antidepressants for ‘other’ indications.....	18
Characteristics associated with antidepressant use.	19
Depression and dementia	20
<i>CONCLUSION</i>	20
TABLES & FIGURES.....	22
TABLE I.....	22
TABLE II.....	23
TABLE III.....	24
TABLE IV.....	25
TABLE V.....	26
FIGURE 1.....	27

ABSTRACT

Background & objectives:

Since antidepressants are prescribed for multiple indications, the use of an antidepressant cannot be equated with a diagnosis of depression.

The objective of this study was to examine the quality of antidepressant prescribing in Belgian nursing homes with a critical evaluation of indications and dosages: to see whether depression was appropriately treated in terms of drug choice, indications and/or under-dosing.

Methods:

Clinical and medication data was obtained from a cross-sectional study of a representative stratified random sample of 1730 residents from 76 Belgian nursing homes (PHEBE study 2006). A 28-item checklist of clinical conditions was ad hoc designed for the PHEBE study and sent to the general practitioner (GP) to collect clinical information. We copied the medication chart, classified the drugs into codes with the Anatomical Therapeutic and Chemical classification system, and transferred the drug names and dosages into a database. Information on indications was retrospectively obtained from the GP, so that we could link the indication to each medication. Minimal effective doses (MED) of antidepressants to treat major depression were obtained from literature to assess under-dosing.

Results:

The overall use of antidepressants in nursing homes was 39.5% [95%CI, 37.2-41.8]. The physicians labelled 34.2% [95% CI 32.0-36.4] of the residents as having a depression and 80.9% of them were treated with an antidepressant.

Indications among the single antidepressant users (n= 551) were 'depression' (66.2%), 'insomnia' (13.4%), 'anxiety' (6.2%) and 'neuropathic pain' (1.6%).

In the indication of 'depression', 74.8% used a Selective Serotonin Reuptake Inhibitor (SSRI), predominantly citalopram, sertraline and escitalopram. Venlafaxine was used by 10.7% of the residents. Dosages for these antidepressants were equal to or higher than the MED. But when trazodone, amitriptyline or mirtazapine was used to treat depression, respectively 92.3%, 55.5% and 44.5% was dosed under the MED.

In the indication of 'insomnia' most of the time trazodone (90.5%) or mirtazapine (5.4%) was used and in lower dosages than required for depression treatment (<MED). Tricyclic antidepressants were predominantly used for the treatment of neuropathic pain and also at lower dosages. Of all the residents receiving a medication for 'anxiety', only 13.9% received an antidepressant (mostly a SSRI), and the remaining received a benzodiazepine.

Conclusion:

The number one indication for the use of an antidepressant was depression. Within this indication, mostly the recommended SSRIs were used in dosages equal to or higher than the MED. Furthermore, we noticed that there was a substantial use of sedative antidepressants for insomnia and that the physicians preferred the use of benzodiazepines over the recommended SSRIs to treat anxiety chronically.

ORIGINAL RESEARCH ARTICLE

INTRODUCTION

The prevalence of late-life depression in nursing homes varies from 11% to 50% ^[1-5] and is generally higher than in community dwelling older adults ^[6]. Depression is often reported to be under-recognised and undertreated in older adults ^[3, 7]. However, the use of antidepressants (ADs) increased over the last decade ^[8] and this trend was also visible in the nursing home population ^[9, 10].

Depression often has an atypical presentation in older adults ^[11]. The poor recognition of clinical features of depression in old age and the overlap with symptoms of dementia or other co-morbidities makes a correct diagnosis difficult.

Depression negatively affects daily activities ^[12], the quality of life ^[13], causes high treatment and societal costs ^[14, 15] and increases mortality ^[16]. Chronic diseases, pain and social deprivation are known risk factors for developing a depression ^[17]. These elements are common in long-term care facilities.

Moreover, transition from the community to a nursing home can trigger depression, which results in the high number of newly admitted residents developing a depression ^[2, 18].

Depression is a treatable illness ^[19]; approximately 50-60% patients with major depressive disorder are thought to improve clinically as a consequence of antidepressant treatment ^[20, 21]. In addition, there are other indications to prescribe an antidepressant. Anxiety, panic disorders, behavioural and psychological symptoms of dementia and neuropathic pain ^[22] are the potential indications of antidepressant prescribing in the older population. In daily practice, antidepressants are also prescribed for insomnia without concomitant depressive symptoms, although this indication is not mentioned in the official labelling ^[23].

In order to make a profound evaluation of the antidepressant prescribing attitude and to evaluate the pharmacotherapy of depression, both indication and dosage information are necessary. Drug utilisation

studies that evaluate the indication and dosages of these medications are scarce^[24-26]. In these studies, indication analysis is mostly done by linking clinical diagnoses (ICD-9 or DSM IV) and medication databases. This does not automatically provide information for which reason/indication each antidepressant is prescribed. Similar to the BEACH project in Australia^[27], the PHEBE study (Prescribing in Homes for the Elderly in Belgium) was designed to include the indication per medication as indicated by the prescribing general practitioner (GP). The PHEBE study was a cross-sectional, descriptive study of a representative stratified random sample of 76 Belgian nursing homes, investigating the overall drug utilisation in Belgian nursing homes in 2006. A detailed description of the methods and findings of this study was published elsewhere^[28-30].

The objective of this subanalysis of the data obtained in the PHEBE study was to examine the quality of antidepressant prescribing in Belgian nursing homes with a critical evaluation of indications and dosages: to see whether depression was appropriately treated in terms of drug choice, indications and/or underdosing. An additional objective was to investigate the resident characteristics associated with antidepressant use.

METHODS

Setting

Belgium has a mixed, public/private health care system. The system works on a fee for service base. The Belgian long-term residential care structure consists of residential and/or nursing homes for older people, which offer a home replacement with or without nursing care. Governance of nursing homes for older people is either public (community health services) or private (predominantly non-profit) with little difference in quality. In Belgian nursing homes, residents are still supervised by their own GP, and this leads to an average of 32 GPs per nursing home.

Data collection

In the PHEBE study, data collection at resident level included administrative, clinical and medication data. We obtained the medication data by copying the medication chart, transferring and coding it to a database. For collecting clinical data, we sent the GP a checklist with 28 items, focusing on clinical problems (i.e. cardiovascular disease, COPD, peptic ulcer) as well as focusing on care problems (i.e. problems with a predominant nursing care burden, such as dementia, insomnia, depression,...). The 28-item checklist of clinical conditions was ad hoc designed for this study, with the items selected based on existing prescribing quality indicators (BEERS^[31], ACOVE^[32], BEDNURS^[33]) for older adults. The diagnosis of depression is in this study based on the clinical evaluation by the GP. In Belgium, the KATZ scale is a mandatory instrument in the nursing homes and it consist of two parts. The first part scores activities of daily living (ADL) and the second part scores disorientation in time and place. This second part is scored from 1 (no disorientation) to 5 (severe) and used as a proxy to estimate the severity of dementia in this study. Residents receiving palliative care were excluded from analysis.

Classification of Antidepressants

Antidepressants were classified according to the Anatomical Therapeutic Classification system (ATC)^[34].

According to the availability on the Belgian pharmaceutical market, we investigated the classes N06AA

Tricyclic Antidepressants (TCA), N06AB Selective Serotonin Reuptake Inhibitors (SSRI), N06AG Mono Amino Oxidase Inhibitors (MAO-I) and the class N06AX which includes serotonin-norepinephrine reuptake inhibitors and other antidepressants.

The SNRI, duloxetine, and bupropion are not included in the analysis because they were not yet commercialised in Belgium in 2006. Lithium, in ATC considered as an antipsychotic and mostly used to treat bipolar disorders, was excluded from analysis. Combination drugs of an antidepressant and an antipsychotic were also excluded. Duplicate use therapy was defined as the concomitant use of 2 or more ADs. Medication prescribed in short term and as-needed medications were excluded from analysis. We focused on chronic use (defined as daily use for at least 3 months).

We analysed 2 levels of describing AD use: the prescription (medication) and the resident level.

Indications were analysed at prescription and resident level and dosages at prescription level only.

Indication and dosages

Data on indications were collected retrospectively: the GP received a printout of the resident's medication chart for verification of the medication use, and he/she was asked to tick relevant indications from a predefined list for ADs: depression, posttraumatic stress, anxiety, insomnia, neuropathic pain or other.

The prescribed daily dose (PDD) of each AD was recorded by summing the doses taken at the different moments of intake during one day. To interpret these doses, we chose the universal Defined Daily Dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults^[34]. We described the distribution of the PDD using its median and range. To examine possible under-dosing in the treatment of *depression*, we used the Minimal Effective Dose (MED). The MED of an antidepressant serves as a threshold, below which all doses are not effective in treating major depressive episode^[35]. The MED of the most common antidepressants were determined using *the Prescribing*

guidelines^[36] and *Pharmacotherapy: A pathophysiologic Approach*^[37]. We considered under-dosing when the PDD of the antidepressant was under the MED.

Statistical analysis.

The data was analysed using the statistical package SPSS version 18. The alpha level of significance was set at $p < 0.05$. We used descriptive statistics to explore indications and dosages.

We examined the characteristics (demographical, clinical, medication and institutional information) of the AD users and the nonusers, and also compared characteristics of the AD users for the different indications (respectively for depression and all other indications). To investigate differences, we used χ^2 for discrete variables, t-tests for continuous variables or non-parametric statistics (Mann-Whitney U test) for skewed distributions.

In a second analysis, we explored a risk profile for AD use. We calculated the Odds ratios and the 95% confidence intervals in univariate and multivariate analysis. For multivariate analysis, we used a stepwise regression model including the statistical significant variables from the univariate analysis.

RESULTS

Study population characteristics.

Medication data and clinical information of 1730 nursing home residents was included in the analysis.

The mean age was 85 (range 60-104) and 78.1% was female. The prevalence of depression was 34.2%[95% CI 32.0-36.4]. In 14.9% of the residents a combination of depression and dementia was noted.

The mean number of chronic medication per resident was 7, ranging from no medication (in less than 1% of the residents) to 22. The most frequently used drugs among the residents were the central nervous system drugs, with benzodiazepine, antidepressant, antipsychotic and anti-dementia drug prevalence in respectively 53.1%, 39.5%, 32.9% and 8.3% of all residents. The demographical and clinical characteristics of the study population are shown in table I.

Antidepressant use at Resident level: prevalence and indications.

The prevalence of chronic AD utilisation among 1730 residents was 39.5%[95% CI 37.2-41.8]. The use of a single AD was seen in 32.6% , while the concomitant use of 2 to 4 ADs was found in 6.9%. Among the antidepressant users, using a single AD (n=551), the leading indication for this use was 'depression' (66.2%), followed by 'insomnia' (13.4%), 'anxiety' (6.2%) and 'pain' (1.6%). We found the use of a single AD for 'multiple indications' in 11.6%. It consisted largely of depression associated with another indication (Table II).

The physicians labelled 34.2% [95% CI 32.0-36.4] of the residents as depressed and 80.9% of them were treated with an AD; more specific indication analysis showed that 73.1% of the residents with noted depression received an AD for that very indication (Table II).

Table III shows which AD was most used for which indication. When the indication of the AD was 'depression', 74.8% of the residents took a SSRI, 10.7% venlafaxine and 8.2% mirtazapine. For the single

indication 'insomnia' and for the combination of 'insomnia and depression', in respectively 90.5% and 53.3% trazodone was used. When the indication of the AD was 'anxiety', different AD classes were used, but mostly SSRIs (64.7%), trazodone (14.7%) and venlafaxine (8.8%). Of all residents receiving a medication for anxiety only 13.9% received an AD (mostly an SSRI) and the remaining received a benzodiazepine. The indication of 'neuropathic pain' was mostly treated with TCA (66.7%) (Table III).

Antidepressant use at Prescription level: prevalence and dose analysis.

The most frequently prescribed class of all 814 AD prescriptions was SSRI (52.8%) with citalopram, sertraline and escitalopram accounting for respectively 17.1%, 14.5% and 10.2%. Trazodone, which is a serotonin modulator, was the most prescribed molecule (22.9%). Venlafaxine was found in 8.2% and mirtazapine was found in 7.7% of all AD prescriptions. The TCA group accounted for 5.8% with amitriptyline (3.6%) as the most representative TCA drug. MAO-I prescriptions were negligible (0.1%) (Table IV).

Of the 814 prescriptions, 72.5% was indicated for *depression*. Table IV shows the frequency of use of all ADs and dosing information of the most common ADs for this indication. The amount of prescriptions with PDD below the MED for the treatment of depression was high for trazodone (92.3%), amitriptyline (55.5%), and mirtazapine (44.5%). We did not observe this under-dosing when an SSRI or venlafaxine was prescribed.

When we used the DDD as a reference, we saw that for the indication of *insomnia*, the physicians prescribed daily dosages below the DDD (98.2%); this was also the case for the treatment of (*neuropathic pain*) (87.5%). For *anxiety*, mostly 1 DDD (53.8%) or less than 1 DDD was prescribed (46.2%).

Characteristics associated with AD use.

Univariate analysis showed that AD use was significantly associated with polypharmacy, peptic ulcer and some care problems such as depression, insomnia, pain and constipation. We registered a gradual decrease in AD use from the age of 80. In a public nursing home and where the medication was dispensed through a hospital pharmacy, there was less AD use (Table V).

In multivariate analysis, AD use was more frequent in younger residents (OR 0.97, 95% CI 0.96-0.99), in residents with insomnia (OR 1.59, 95%CI 1.26-2.01) and in private nursing homes (OR 1.54, 95%CI 1.25-1.90). AD use was also more likely in residents with more chronic use of medications (OR 1.15 95%CI 1.11-1.19), concomitant use of benzodiazepines (OR 1.28, 95%CI 1.00-1.62), antipsychotics (OR 1.26, 95%CI 1.01-1.57), anti-dementia medication (OR 1.54, 95%CI 1.07-2.23) and antiparkinson medication (OR 1.58, 95%CI 1.14-2.18) (Table V).

Characteristics associated with Antidepressant use for the indication 'depression' and 'other' indications.

Residents who received an AD for the indication of depression had more chronic obstructive pulmonary disease and had a significant larger usage of (chronic) medication in comparison to the residents that received an AD for other indications. The residents that received an AD for other indications were more likely to be labelled by their physician as insomniacs (Table V).

Depression and dementia

In more than one third (34.4%) of the nursing home residents with some form of dementia, the GP recorded depression. The prevalence of noted depression as well as the use of an AD for the indication depression decreased as dementia progressed. On the other hand, the proportion of AD use for other indications slightly increased in patients with more advanced dementia (Figure 1).

DISCUSSION

To our knowledge, our study is the first European study to collect indication and dosage information of each antidepressant directly from the treating physician. Based on our results, we cannot state that depression is undertreated in the Belgian nursing homes. More than one third of Belgian nursing home residents were labelled with depression and 81% of them were treated with an AD. The prescribing physicians used suitable drug classes according to the guidelines for depression in older people ^[38]. Under-dosing was not seen in the treatment of depression with the most prevalent AD classes, but when ADs were used for other indications, we saw the use of lower doses.

There was a substantial use of ADs (mainly trazodone) for insomnia. Furthermore, we noticed physicians were more likely to prescribe a benzodiazepine rather than the preferred SSRIs to treat (chronic) anxiety.

STRENGTHS AND LIMITATIONS

Our sample has proved to be representative both on institutional and on residential level^[39]. Moreover, the large size of our sample makes it possible to extrapolate our findings to the entire Belgian nursing home setting. Similar prevalence numbers of depression and AD use were found in European ^[1, 40] and American ^[9] studies, but for specific indication and dosage evaluation, no identical studies were available. The indications of AD prescribing were retrospectively collected by interviewing the GP. As the GP is the prescriber of the AD, this approach gives us a clearer view of the use of ADs rather than linking clinical diagnoses and medication databases. This strength can be a limitation as well due to the retrospective aspect. Our interpretation of under-dosing and the MED as a threshold was established by using a strict methodology (see methods).

A limitation of our study is that we did not collect information about alternative treatment strategies for depression such as psychotherapy, so we focus our discussion on the residents receiving an AD. Another

limitation is that we did not use validated diagnostic criteria to evaluate (severity) of depression and dementia, but we relied on the a posteriori clinical judgement of the treating physician. The physicians should have been aware that depression is not equal to depressive mood, but we don't know whether they had fully considered this. Moreover, we had no breakdown of various degrees of depression in our checklist of clinical diagnoses. The disorientation axes of the KATZ scale may not be an ideal dementia grading instrument as it can be influenced by other disorders (depression, delirium). However, we decided to use this tool for pragmatic reasons, because it is mandatory in the Belgian context, and thus the data are readily available. In addition, in this cross-sectional study, we were not able to investigate the distribution of the duration of AD use nor was it possible to investigate temporal changes and the relationship between process and outcome. Furthermore, we reduced the complexity of the analysis by narrowing our in depth analysis of indications to single AD users, and we disregarded residents on more than one AD (6.9% of all residents).

DISCUSSION of the MAIN FINDINGS

According to our study, in more than one third of the Belgian nursing home residents the treating physician noted depression. This percentage is situated in the middle segment of the prevalence range 11%-50% reported in other studies in different western countries ^[1, 3-5]. Of all the residents labelled with depression, 81% was treated with an AD and 73% received an AD especially for the indication depression. Knowing that only major depressions should be treated pharmacologically, our results do not support the hypothesis of undertreatment in the group of residents with noted depression. Other recent articles also indicate an AD treatment percentage of more than 80% ^[9, 40] for depressed residents, but these percentages are irrespective of indication. In addition to reporting that there is no undertreatment, it could also be useful to examine the reason why about a third of all residents need a pharmacological treatment of their depression.

In our study, more than one quarter of the AD prescriptions (28%) was not to treat depression. Other approved indications such as anxiety and neuropathic pain accounted for 7.8% of all AD use. Insomnia without depressive symptoms accounted for 13.4%.

Most of the ADs were prescribed at a dosage of 1 DDD or less and rarely exceeded 1 DDD. Possible depression under-dosing in the nursing home population was checked by analysing the prescribed daily dose in accordance to the MED. The SSRI group and venlafaxine were dosed above their MED.

Trazodone, TCAs and mirtazapine were often dosed under their MED. It is important to keep in mind that when treating older adults, polypharmacy, polypathology, pharmacokinetic and –dynamic alterations can influence dosage response. The MED does not really consider these particular changes in determining the threshold. In literature, there is not much guidance on dosing of antidepressants in frail older adults; slow upwards titration and close monitoring of side-effects is recommended ^[41].

Antidepressants for the indication ‘depression’

For the indication of depression in old age, SSRIs deserve a preference within the pharmacological approach ^[38, 42] and as found in our study, were the most commonly prescribed ADs in Belgian nursing homes (citalopram, sertraline, escitalopram). Although SSRIs have a more appropriate side-effect profile and are safer in over-dose for older adults than other antidepressants, still, physicians should prescribe these drugs with caution, because of the risk of drug-drug interactions and adverse effects such as hyponatraemia^[43], upper gastrointestinal bleeding^[44], insomnia, restless leg syndrome, agitation and the potential risk of serotonin syndrome^[45, 46]. The BEERS list ^[31] discourages the use of fluoxetine in older adults, due to its long half-life and inhibition of cytochrome P 450 enzymes (mainly CYP2D6). In our study this SSRI was prescribed only in 2% of the cases.

In our study, venlafaxine was also frequently prescribed for depression. Together with the SSRIs, it is known for its stimulating properties that can cause sleeplessness ^[47]. Venlafaxine should be reserved as a

second-line treatment for depression and is not indicated in patients with heart failure, coronary disease and uncontrolled hypertension ^[38].

Mirtazapine is also a relatively often prescribed AD for older adults because it has less anti-cholinergic side effects (i.e. dry mouth, urinary retention, constipation) than TCAs ^[48].

TCAs, equally effective as SSRIs ^[49], are known for their toxicity in overdose ^[50] and their anti-cholinergic side-effect profile. Therefore, they are not recommended as a first choice to treat depression in older adults. However, a recent cohort study concluded that SSRIs and the newer ADs were associated with a higher risk of adverse events, such as stroke, fracture and all-cause mortality, compared with TCAs ^[40].

In our study, SSRIs and venlafaxine are prescribed above the MED. However, 45% of the mirtazapine, 96% of the trazodone and 56% of the TCA prescriptions are dosed under their MED, a possible precaution of prescribers aware of the sedative and/or anti-cholinergic properties of these drugs.

Antidepressants for 'other' indications

The most frequently prescribed AD in this setting was trazodone. It was predominately prescribed at lower dosages for primary insomnia. The use of trazodone for sleep disturbance in adult and older patients is extensive in clinical practice ^[51]. In depressed adult patients, there is evidence for the efficacy of trazodone for sleep disturbance ^[52]. In non-depressed adult patients, trazodone might be effective in primary insomnia^[53]. However, the evidence for its use for primary insomnia in older people is rather scarce ^[23] and controversial ^[54]. Trazodone has so far not received an indication as sleep-promoting agent in the official labelling. The side effects of trazodone are not very different from other (non)benzodiazepine hypnotics in terms of residual daytime impairments, but priapism and orthostatic hypotension are important side effects of trazodone ^[55].

The amount of trazodone prescriptions intended for insomnia and not to treat depression is increasing ^[51, 56]. The (inter)national warnings and campaigns against the chronic use of benzodiazepines (OBRA

'87)^[57] ^[15] are a possible reason for the preferential prescribing of trazodone. Another consideration can be the relatively lower cost of trazodone in Belgium in comparison to (non)benzodiazepine hypnotics. Moreover, trazodone, unlike (non)benzodiazepines hypnotics, is reimbursed (for 75%) by the Belgium Health Care system. In order to maintain a healthy economic situation, it is important to ensure that no shift towards reimbursed sedative ADs takes place, particularly in the absence of convincing evidence.

Another indication for which an AD can be prescribed is neuropathic pain. Our study confirmed the assumption that TCAs are mostly prescribed for the treatment of pain ^[22], and at doses lower than the DDD ^[24]. Although not licensed for this indication, amitriptyline, which was in our study the most prevalent agent, is considered first-line treatment for neuropathic pain in guidelines^[58]. Duloxetine is also indicated for neuropathic pain and is registered for this indication ^[58].

Although the first pharmacological choice to treat anxiety disorders chronically is a SSRI ^[59, 60], in our study physicians were more likely to prescribe a benzodiazepine on a chronic base rather than an AD. Benzodiazepines can be used for acute anxiety or can be co-administered for a short period of time (max 4 weeks) to overcome the delayed pharmacological effect of the AD ^[59, 61, 62]. However, to avoid tolerance and dependence, this dual therapy should be tapered in time.

Characteristics associated with antidepressant use.

We found that older residents had a lower AD use. This is also mentioned in other AD studies ^[9, 17] and with other medication groups. This can be partly explained by the increasing incidence of dementia in older residents and the growing inability of residents to utter specific complaints (feeling depressed) with deepening dementia. We also found that psychotropic use and polypharmacy are inextricably linked, indicating the need for clinical practice guidelines and education focusing on initiation and reassessment of ADs and psychotropic use in general. Antiparkinson drugs were significantly associated with AD use which can be explained by the symptoms of Parkinsonism: depression is a common

neuropsychiatric manifestation in Parkinson's disease. As ADs may have sedative properties and are often used for the treatment of insomnia, it was no surprise that insomnia was correlated with AD use, and more specifically with AD use for other indications than depression. Because in Belgium the differences in institutional characteristics between a private and public nursing home are little, we cannot explain the association between the private nursing homes and the elevated likelihood of receiving an antidepressant.

Depression and dementia

In our study, in one third of the residents with noted dementia, also a depression was reported. This is higher than the prevalence rate in other European countries ^[5, 63] and the United States ^[64]. When analyzing the different stages of disorientation (expression of dementia), we found that both the prevalence of depression and the antidepressant use decreased with worsening disorientation. This could indicate the difficulty to diagnose depression in cognitive impaired residents and a possible under-treatment in this specific patient group. However, a recent publication in the Lancet ^[65] suggested the absence of benefit of antidepressants in dementia compared to placebo and the increased risk of adverse events. The trial does not advocate the abandonment of antidepressants but underscores the need to think about creative, but evidence-based alternatives (such as psychosocial interventions) for the management of depression in people with dementia. But due to organizational- and staffing problems psychotherapy is not routinely available in Belgian nursing homes.

CONCLUSION

ADs were used by 39.5% of the residents. Overall, the quality of AD prescribing in the Belgian nursing homes is relatively satisfactory. Most of the residents with reported depression were treated according to evidence-based recommendations with SSRIs (mainly citalopram, sertraline and escitalopram) in dosages equal to or higher than the MED. Venlafaxine, not the first-choice drug in the older population,

was used in 1/10 and in dosages equal to or higher than the MED. All other antidepressants (TCAs, mirtazapine, trazodone) used for depression were dosed under the MED.

In the indication of anxiety, most of the time, the physicians did not prescribe the recommended SSRIs, but they preferred the chronic use of benzodiazepines.

A controversial issue is the prescribing of sedative ADs (mostly trazodone) for insomnia (13.4%). A plausible explanation for this prescribing without clear evidence of efficacy and safety in frail older adults can be found in the reimbursed status of ADs and the relatively lower cost of trazodone in comparison to other sleeping pills.

TABLES & FIGURES

TABLE I

Characteristics of the study population

RESIDENT CHARACTERISTICS	total population n= 1730
<i>Demographical characteristics</i>	
Age (mean + range)	84.8 [60-104]
Gender (% female)	78.1
<i>Main Clinical problems(%)</i>	
Cardiovascular	75.7
Peptic ulcer	24.6
COPD	17.2
Diabetes	16.8
Renal failure	12.6
Hepatic problems	1.4
Parkinson	8.3
<i>Main Care problems(%)</i>	
Dementia	47.7
Depression	34.2
Insomnia	44.0
Risk of falling	45.5
Constipation	41.9
Chronic pain	35.1
Incontinence	35.9
<i>Medication Information</i>	
Number of (mean + range)	
Medications	8.0 [0-22]
Chronic Medications	7.1 [0-22]
Use of Psychotropics (%)	
Benzodiazepines/z-drugs	53.1
Antidepressants	39.5
Antipsychotics	32.9
Use of Antidementia drugs(%)	8.3
Use of Antiparkinson drugs(%)	10.9

TABLE II**Prevalence of Antidepressant (AD) use and Depression and the distribution of users per indication.**

Prevalence	n	%
total AD use (N=1730)	684	39.5
single AD use	565	32.6
multiple AD use	119	6.9
total prevalence of depression (N=1730)	591	34.2
AD use among residents with depression (N=591)	478	80.9
AD use specific for the indication depression among residents with depression (N=591)	432	73.1
Indications among single AD users (N=551*)	n	%
Depression	365	66.2
Insomnia	74	13.4
Anxiety	34	6.2
Pain	9	1.6
Multiple indications	64	11.6
depression+ insomnia	22	4.0
depression+ anxiety	23	4.2
depression + pain	8	1.5
Other indications	5	0.9

*total residents receiving a single AD(n=565) corrected for 14 missing indications

TABLE III

Distribution of Indications of (single) antidepressant (AD) use in Belgian nursing home residents (at resident level).

ANTIDEPRESSANT	INDICATIONS for Antidepressant use among nursing home residents*				
	Depression n= 365	Insomnia n= 74	Anxiety n= 34	Pain n=9	Multiple n=64
TCA (=N06AA)	8 (2.2%)	1 (1.4%)	2 (5.9%)	6 (66.7%)	4 (6.2%)
Amitriptyline	3 (0.8%)		2 (5.9%)	5 (55.6%)	
SSRI (=N06AB)	273 (74.8%)	1 (1.4%)	22 (64.7%)	1 (11.1%)	30 (46.9%)
Citalopram	91 (24.9%)	1 (1.4%)	5 (14.7%)	1 (11.1%)	7 (10.9%)
Sertraline	67 (18.4%)		7 (20.6%)		9 (14.1%)
Escitalopram	60 (16.4%)		3 (8.8%)		3 (4.7%)
Paroxetine	39 (10.7%)		7 (20.6%)		10 (15.6%)
Fluoxetine	16 (4.4%)				1 (1.6%)
MAO-I (=N06AG)	1 (0.3%)				
OTHERS (=N06AX)	83 (22.7%)	72 (97.3%)	10 (29.4%)	2 (22.2%)	30 (46.9%)
Trazodone	10 (2.7%)	67 (90.5%)	5 (14.7%)	1 (11.1%)	18 (28.1%)
Venlafaxine (=SNRI)	39 (10.7%)		3 (8.8%)		6 (9.4%)
Mirtazapine	30 (8.2%)	4 (5.4%)	1 (2.9%)	1 (11.1%)	4 (6.3%)

*n=551 (single AD users corrected for 14 missing indications); The indication 'others' is not shown (n=5)

AD used by less than 10 residents are not shown:

TCA: dosulepine, imipramine, clomipramine, doxepine, nortriptyline, maprotiline

OTHERS: mianserine, reboxetine, hypericum perforatum and moclobemide (MAO-I)

TCA= Tricyclic Antidepressant; SSRI= selective serotonin reuptake inhibitor; MAO-I=monoamino oxidase inhibitor

TABLE IV

Distribution of Antidepressants (AD) prescribed in Belgian nursing homes and dose information for the indication 'depression' (at prescription level)

ANTIDEPRESSANTS	TOTAL number of Prescriptions (n=814)	Prescriptions for depression (n= 590)	PDD median (range)	MED	number of prescriptions indicated for depression below MED
TCA (=N06AA)	47 (5.8%)	22 (3.7%)			
Amitriptyline	29 (3.6%)	9 (1.5%)	25mg (10-50)	50mg	5 (55.5%)
SSRI (=N06AB)	430 (52.8%)	386 (65.4%)			
Citalopram	139 (17.1%)	128 (21.7%)	20mg (10-40)	20mg	16 (12.5%)
Sertraline	118 (14.5%)	103 (17.5%)	50mg (10-100)	50mg	9 (8.9%)
Escitalopram	83 (10.2%)	77 (13.1%)	10mg (5-20)	10mg	15 (19.5%)
Paroxetine	69 (8.5%)	58 (9.8%)	20mg (10-40)	10mg	0
Fluoxetine	22 (2.1%)	20 (3.4)	20mg (10-20)	10mg	0
OTHERS (=N06AX)	336 (41.3%)	181 (30.7%)			
Trazodone	186 (22.9%)	52 (8.8%)	100mg (50-150)	150mg	48 (92.3%)
Venlafaxine	67 (8.2%)	61 (10.3%)	75mg (37.5-300)	75mg	3 (4.9%)
Mirtazapine	63 (7.7%)	54(9.2%)	30mg (7.5-30)	30mg	24 (44.5%)

ADs with less than 10 prescriptions are not shown:

MAO-I: Moclobemide n=1

TCAs: Dosulepine n=8, Imipramine n=4, Clomipramine n=2, Doxepine n=2, Nortriptyline n=1, Maprotiline n=1

OTHERS: Mianserine n=10 ; Reboxetine n=5; Hypericum=5;

PDD= prescribed daily dose (for depression); MED= Minimum Effective Dose (for depression)

TCA= Tricyclic Antidepressant; SSRI= selective serotonin reuptake inhibitor; MAO-I=monoamino oxidase inhibitor

TABLE V

Factors associated with Antidepressant use (AD).

CHARACTERISTICS	NON user N=1046	ANTIDEPRESSANT user		for other indications N= 162	p *	RISK CALCULATION**	
		Total N= 684	for depression N= 522			UNIVARIATE OR(95% CI)	MULTIVARIATE OR(95% CI)
<i>Demographical characteristics</i>							
Age (mean + range)	85.7 [60-104]	83.5 [60-102]	83.5 [60-102]	83.6 [60-102]	0.897	0.97(0.96-0.98)	0.97(0.96-0.99)
Gender (% female)	77.6	78.4	80.1	74.7	0.143	1.03(0.82-1.31)	
<i>Main Clinical problems(%)</i>							
Cardiovascular	75.0	75.8	77.4	74.7	0.477	1.09(0.81-1.26)	
Peptic ulcer	22.1	27.8	29.6	24.7	0.230	1.33(1.07-1.67)	
COPD	16.0	18.9	20.9	13.0	0.024	1.22(0.95-1.57)	
Diabetes	16.3	17.4	18.7	14.8	0.264	1.06(0.82-1.37)	
Renal failure	12.3	12.8	13.1	13.0	0.977	1.05(0.77-1.37)	
Hepatic problems	1.2	1.6	1.5	1.9	0.780	1.25(0.56-2.80)	
Parkinson	7.3	9.8	10.8	7.4	0.212	1.36(0.97-1.91)	
<i>Main Care problems(%)</i>							
Dementia	47.3	48.0	47.0	52.8	0.202	1.02(0.84-1.24)	
Depression	11.5	70.3	84.2	29.2	p<0.001	18.07(13.99-23.34)	***
Insomnia	36.1	54.8	52.7	66.7	0.002	2.09(1.72-2.55)	1.59(1.26-2.01)
Risk of falling	43.9	47.8	48.6	45.6	0.516	1.17(0.97-1.42)	
Constipation	39.1	45.3	45.1	49.7	0.306	1.27(1.04-1.54)	
Chronic pain	32.6	38.3	40.8	32.7	0.066	1.27(1.04-1.55)	
Incontinence	34.6	37.3	36.0	43.5	0.089	1.12(0.91-1.35)	
<i>Medication Information</i>							
Number of (mean + range)							
Medications	7.1 [0-22]	9.2 [1-22]	9.5 [2-22]	8.9 [2-22]	0.012	1.15(1.12-1.18)	***
Chronic Medications	6.3 [0-22]	8.1 [0-22]	8.5 [2-21]	7.8 [2-19]	0.008	1.18(1.14-1.21)	1.15(1.11-1.19)
Use of Psychotropics (%)							
Benzodiazepines/z-drugs	47.9	63.9	64.6	58.6	0.173	1.99(1.63-2.42)	1.28(1.00-1.62)
Antipsychotics	30.5	38.1	36.4	37.7	0.772	1.47(1.20-1.80)	1.26(1.01-1.57)
Use of Antidementia drugs	8.2	10.4	9.4	5.6	0.126	1.58(1.12-2.22)	1.54(1.07-2.23)
Use of AntiParkinson drugs	9.6	14.9	14.2	9.3	0.104	1.95(1.44-2.64)	1.58(1.14-2.18)
<i>Institutional(%)</i>							
>90 beds	50.8	49.6	49.8	46.3	0.435	0.97(0.90-1.18)	
ownership: private	51.1	60.6	62.1	56.2	0.180	1.47(1.21-1.78)	1.54(1.25-1.90)
linked with hospital pharmacy	17.7	13.0	11.9	16.0	0.166	0.70(0.53-0.92)	

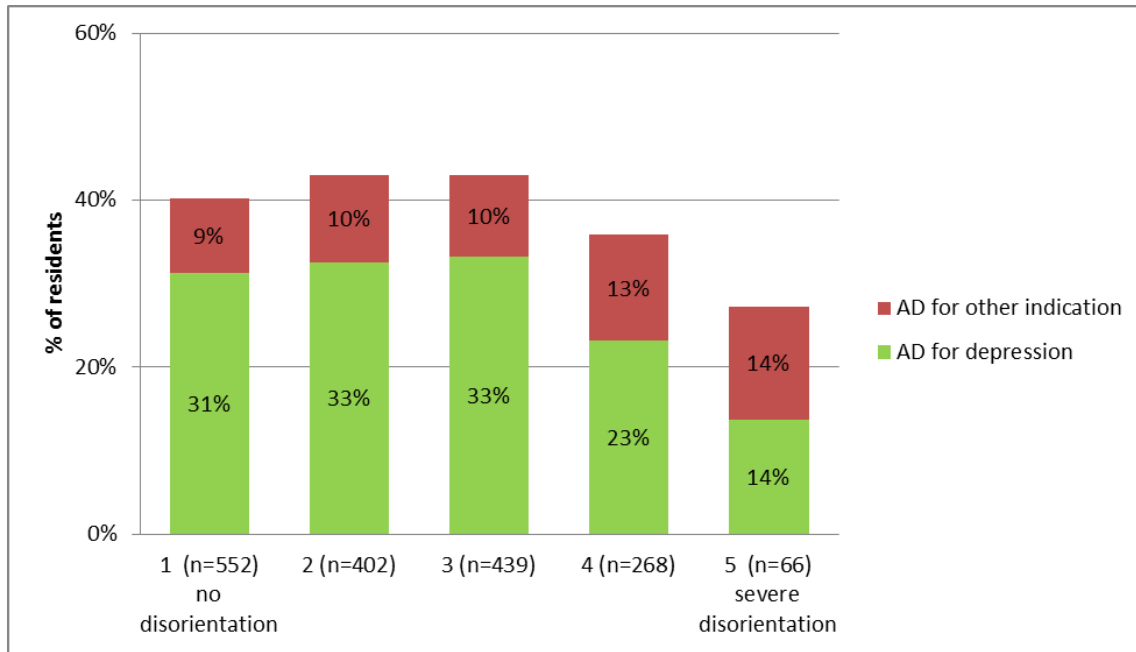
*p value of difference between users for 'depression' and users for 'other' indications , using χ^2 , t-test and Mann Whitney U

**RISK calculation: Risk of receiving an Antidepressant expressed as Odds Ratio (OR)

*** not included in multivariate analysis due to interacting effects

FIGURE 1

Antidepressant use in relation to increasing dementia (scored by the severity of disorientation axes in the KATZ scale)



REFERENCES

1. Kramer D, Allgaier AK, Fejtкова S, et al. Depression in nursing homes: prevalence, recognition, and treatment. *Int J Psychiatry Med.* 2009;39(4):345-58.
2. Achterberg W, Pot AM, Kerkstra A, et al. Depressive symptoms in newly admitted nursing home residents. *International Journal of Geriatric Psychiatry.* 2006 Dec;21(12):1156-62.
3. Brown MN, Lapane KL, Luisi AF. The management of depression in older nursing home residents. *J Am Geriatr Soc.* 2002 Jan;50(1):69-76.
4. Snowdon J, Rosengren D, Daniel F, et al. Australia's use of the Cornell scale to screen for depression in nursing homes. *Australas J Ageing.* 2011 Mar;30(1):33-6.
5. Verkaik R, Francke AL, van Meijel B, et al. Comorbid depression in dementia on psychogeriatric nursing home wards: which symptoms are prominent? *Am J Geriatr Psychiatry.* 2009 Jul;17(7):565-73.
6. Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry.* 1999 Apr;174:307-11.
7. Levin CA, Wei W, Akincigil A, et al. Prevalence and treatment of diagnosed depression among elderly nursing home residents in Ohio. *J Am Med Dir Assoc.* 2007 Nov;8(9):585-94.
8. Akincigil A, Olfson M, Walkup JT, et al. Diagnosis and treatment of depression in older community-dwelling adults: 1992-2005. *J Am Geriatr Soc.* 2011 Jun;59(6):1042-51.
9. Gaboda D, Lucas J, Siegel M, et al. No longer undertreated? Depression diagnosis and antidepressant therapy in elderly long-stay nursing home residents, 1999 to 2007. *J Am Geriatr Soc.* 2011 Apr;59(4):673-80.
10. Hanlon JT, Handler SM, Castle NG. Antidepressant prescribing in US nursing homes between 1996 and 2006 and its relationship to staffing patterns and use of other psychotropic medications. *J Am Med Dir Assoc.* 2010 Jun;11(5):320-4.
11. Fiske A, Wetherell JL, Gatz M. Depression in older adults. *Annu Rev Clin Psychol.* 2009;5:363-89.
12. Drageset J, Eide GE, Ranhoff AH. Depression is associated with poor functioning in activities of daily living among nursing home residents without cognitive impairment. *J Clin Nurs.* 2011 May 18.
13. Hasche LK, Morrow-Howell N, Proctor EK. Quality of life outcomes for depressed and nondepressed older adults in community long-term care. *Am J Geriatr Psychiatry.* 2010 Jun;18(6):544-53.
14. Luppá M, Heinrich S, Matschinger H, et al. Direct costs associated with depression in old age in Germany. *J Affect Disord.* 2008 Jan;105(1-3):195-204.
15. The impact of psychotropics on health with special attention to the elderly. Brussels: Belgium Superior Health Council 2011 Contract No.: 30 October 30.
16. Kane KD, Yochim BP, Lichtenberg PA. Depressive symptoms and cognitive impairment predict all-cause mortality in long-term care residents. *Psychol Aging.* 2010 Jun;25(2):446-52.
17. Karkare SU, Bhattacharjee S, Kamble P, et al. Prevalence and predictors of antidepressant prescribing in nursing home residents in the United States. *Am J Geriatr Pharmacother.* 2011 Apr;9(2):109-19.
18. Hoover DR, Siegel M, Lucas J, et al. Depression in the first year of stay for elderly long-term nursing home residents in the USA. *Int Psychogeriatr.* 2010 Nov;22(7):1161-71.

19. Wilson K, Mottram P, Sivanranthan A, et al. Antidepressant versus placebo for depressed elderly. *Cochrane Database Syst Rev.* 2001(2):CD000561.
20. Schneider LS, Olin JT. Efficacy of acute treatment for geriatric depression. *Int Psychogeriatr.* 1995;7 Suppl:7-25.
21. Hollon SD, Jarrett RB, Nierenberg AA, et al. Psychotherapy and medication in the treatment of adult and geriatric depression: which monotherapy or combined treatment? *J Clin Psychiatry.* 2005 Apr;66(4):455-68.
22. Smith HS, Argoff CE. Pharmacological treatment of diabetic neuropathic pain. *Drugs.* 2011 Mar 26;71(5):557-89.
23. Wiegand MH. Antidepressants for the treatment of insomnia : a suitable approach? *Drugs.* 2008;68(17):2411-7.
24. Nishtala PS, McLachlan AJ, Bell JS, et al. Determinants of Antidepressant Medication Prescribing in Elderly Residents of Aged Care Homes in Australia: A Retrospective Study. *American Journal of Geriatric Pharmacotherapy.* 2009 Aug;7(4):210-9.
25. Hanlon JT, Wang X, Castle NG, et al. Potential Underuse, Overuse, and Inappropriate Use of Antidepressants in Older Veteran Nursing Home Residents. *J Am Geriatr Soc.* 2011 Aug;59(8):1412-20.
26. Preville M, Vasiliadis HM, Bosse C, et al. Pattern of psychotropic drug use among older adults having a depression or an anxiety disorder: results from the longitudinal ESA study. *Can J Psychiatry.* 2011 Jun;56(6):348-57.
27. Henderson J, Harrison C, Britt H. Indications for antidepressant medication use in Australian general practice patients. *Aust N Z J Psychiatry.* 2010 Sep;44(9):865.
28. Elseviers M, VSR, Soenen K., Gobert M., Van Bortel L., Van De Voorde C. Drug utilisation in Belgian nursing homes: impact of residents' and institutional characteristics. *Pharmacoepidemiol Drug Safety.* 2010;19:1041-8.
29. Bourgeois J. EM, Van Bortel L., Petrovic M, Vander Stichele R. . Benzodiazepine use in Belgian nursing homes: a closer look into indications and dosages. *European Journal of Clinical Pharmacology.* 2011.
30. Azermai M. EM, Petrovic M., Van Bortel L., Vander Stichele R. Geriatric drug utilisation of psychotropics in Belgian nursing homes. *Human Psychopharmacology: Clinical and Experimental.* 2011;in press.
31. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. *Arch Intern Med.* 2003 Dec 8-22;163(22):2716-24.
32. Shekelle PG, MacLean CH, Morton SC, et al. Assessing care of vulnerable elders: methods for developing quality indicators. *Ann Intern Med.* 2001 Oct 16;135(8 Pt 2):647-52.
33. Ruths S, Straand J, Nygaard HA. Multidisciplinary medication review in nursing home residents: what are the most significant drug-related problems? The Bergen District Nursing Home (BEDNURS) study. *Qual Saf Health Care.* 2003 Jun;12(3):176-80.
34. WHO. ATC/DDD system. WHO Collaborating Centre for Drug Statistics Methodology; 2009 [30 October 2011]; Available from: <http://www.whocc.no/>.
35. Benkert O, Szegedi A, Wetzel H. Minimum effective dose for antidepressants--an obligatory requirement for antidepressant drug evaluation? *Int Clin Psychopharmacol.* 1996 Sep;11(3):177-85.
36. D. Taylor CP, S. Kapur. Prescribing guidelines 10th edition: informa healthcare; 2010.
37. Dipiro JT. TR, Yee GC., et al. Pharmacotherapy: a pathophysiologic Approach. 5th edition ed. New York: McGraw-Hill Medical 2008.

38. NICE Clinical Guideline: The treatment and management of depression in adults. London: National Institute for Health and Clinical Excellence; 2009 [10 August 2011]; Available from: <http://www.nice.org.uk/nicemedia/live/12329/45888/45888.pdf>.
39. Elseviers MM, Vander Stichele RR, Van Bortel L. Drug utilization in Belgian nursing homes: impact of residents' and institutional characteristics. *Pharmacoepidemiol Drug Saf.* 2010 Oct;19(10):1041-8.
40. Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *Bmj.* 2011;343:d4551.
41. Kennedy GJ, Marcus P. Use of antidepressants in older patients with co-morbid medical conditions: guidance from studies of depression in somatic illness. *Drugs Aging.* 2005;22(4):273-87.
42. Petrovic M, De Paepe P, Van Bortel L. Pharmacotherapy of depression in old age. *Acta Clin Belg.* 2005 May-Jun;60(3):150-6.
43. Movig KL, Leufkens HG, Lenderink AW, et al. Serotonergic antidepressants associated with an increased risk for hyponatraemia in the elderly. *European Journal of Clinical Pharmacology.* 2002 May;58(2):143-8.
44. Andrade C, Sandarsh S, Chethan KB, et al. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry.* 2010 Dec;71(12):1565-75.
45. Schellander R, Donnerer J. Antidepressants: clinically relevant drug interactions to be considered. *Pharmacology.* 2010;86(4):203-15.
46. Draper B, Berman K. Tolerability of selective serotonin reuptake inhibitors: issues relevant to the elderly. *Drugs & Aging.* 2008;25(6):501-19.
47. Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. *Hum Psychopharmacol.* 2005 Dec;20(8):533-59.
48. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. *J Am Geriatr Soc.* 2008 Jul;56(7):1333-41.
49. Mottram P, Wilson K, Strobl J. Antidepressants for depressed elderly. *Cochrane Database Syst Rev.* 2006(1):CD003491.
50. Hawton K, Bergen H, Simkin S, et al. Toxicity of antidepressants: rates of suicide relative to prescribing and non-fatal overdose. *Br J Psychiatry.* 2010 May;196(5):354-8.
51. Roy AN, Smith M. Prevalence and cost of insomnia in a state Medicaid fee-for-service population based on diagnostic codes and prescription utilization. *Sleep Med.* 2010 May;11(5):462-9.
52. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, et al. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. *Prog Neuropsychopharmacol Biol Psychiatry.* 2002 Feb;26(2):249-60.
53. Roth AJ, McCall WV, Liguori A. Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. *J Sleep Res.* 2011 May 30.
54. Conn DK, Madan R. Use of sleep-promoting medications in nursing home residents : risks versus benefits. *Drugs & Aging.* 2006;23(4):271-87.
55. Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psychiatry.* 2005 Apr;66(4):469-76.
56. James SP, Mendelson WB. The use of trazodone as a hypnotic: a critical review. *J Clin Psychiatry.* 2004 Jun;65(6):752-5.

57. H. T. Federal Nursing Home Reform Act from the Omnibus Budget Reconciliation Act of 1987. National Long Term Care Ombudsman Resource Center; 2001 [20 October 2011]; Available from: <http://www.allhealth.org/briefingmaterials/obra87summary-984.pdf>.
58. NICE Clinical Guideline: Neuropathic pain. London: National Institute for Health and Clinical Excellence; 2010 [23 August 2011]; Available from: <http://www.nice.org.uk/nicemedia/live/12948/47949/47949.pdf>.
59. B Terluin FBVH, K Van der Meer, et al. Treatment of Anxiety [in Dutch: NHG-Standaarden angststoornissen]. NHG-Standaarden voor huisartsen: Nederlandse huisartsen genootschap; 2009.
60. NICE Clinical Guideline: Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults. National Institute for Health and Clinical Excellence; 2011 [10 August 2011]; Available from: <http://www.nice.org.uk/nicemedia/live/13314/52601/52601.pdf>.
61. Treatment of Anxiety (in Dutch: de aanpak van angst): Belgian Centrum for Pharmacotherapeutic Information (BCFI)2010.
62. Flint AJ. Generalised anxiety disorder in elderly patients : epidemiology, diagnosis and treatment options. *Drugs Aging*. 2005;22(2):101-14.
63. Margallo-Lana M, Swann A, O'Brien J, et al. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. *International Journal of Geriatric Psychiatry*. 2001 Jan;16(1):39-44.
64. Payne JL, Sheppard JM, Steinberg M, et al. Incidence, prevalence, and outcomes of depression in residents of a long-term care facility with dementia. *International Journal of Geriatric Psychiatry*. 2002 Mar;17(3):247-53.
65. Banerjee S, Hellier J, Dewey M, et al. Sertraline or mirtazapine for depression in dementia (HTA-SADD): a randomised, multicentre, double-blind, placebo-controlled trial. *Lancet*. 2011 Jul 30;378(9789):403-11.