

# Duloxetine in the treatment of elderly people with major depressive disorder

## *L'uso della duloxetina nel trattamento degli anziani con disturbo depressivo maggiore*

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**SUMMARY. Introduction.** The elderly population is more frequently subjected to depressive mood compared to the general population and show peculiarities affecting responsiveness; furthermore, aged people need also special care. Duloxetine is a relatively new antidepressant that proved to be effective in adult depression, but has received little attention in elderly populations heretofore. **Aim.** To review the evidence of duloxetine in late-life major depressive disorder (MDD). **Method.** A systematic review of studies focusing on the use of duloxetine in MDD in the elderly has been carried out through the principal specialized databases, including PubMed, PsycLIT, and Embase. **Results.** Only a handful of papers were specifically dedicated to this issue. Duloxetine was found to be effective and safe in old-age MDD, to be better than placebo on many clinical measures in all studies, and to better differentiate from placebo with respect to selective serotonin reuptake inhibitors. Compared to placebo, its side-effect profile is slightly unfavorable and its drop-out rate is slightly higher. Furthermore, when pain is present in old-age MDD, duloxetine is able to reduce it. **Conclusions.** The efficacy and safety of duloxetine in old-age depression are similar to those encountered in adult MDD. There is a relative lack of comparative studies other than with placebo. The special needs of elderly patients with MDD must be addressed with close patient contact to avoid the perils of inappropriate dosing.

**KEY WORDS:** duloxetine, major depressive disorder, pain, old age, antidepressant pharmacotherapy.

**RIASSUNTO. Introduzione.** La popolazione anziana è maggiormente soggetta a umore depresso rispetto alla popolazione generale, con caratteristiche particolari che influenzano la responsività al trattamento farmacologico. Tali pazienti richiedono particolari accorgimenti curativi. La duloxetina è un antidepressivo relativamente nuovo, efficace nella depressione dell'adulto, ma che non ha finora ricevuto sufficiente attenzione per il suo uso nell'anziano. **Scopo.** Passare in rassegna l'evidenza riguardante l'uso della duloxetina nel disturbo depressivo maggiore (DDM) dell'anziano. **Metodo.** È stata condotta una ricerca sistematica di tutti gli studi centrati sull'uso della duloxetina in pazienti anziani con DDM, attraverso le maggiori basi di dati informatiche, quali PubMed, PsycLIT ed Embase. **Risultati.** Sono relativamente pochi i lavori dedicati all'argomento, in base ai quali la duloxetina risulta efficace e ben tollerata nel DDM dell'anziano; inoltre, essa si dimostra, in tutti gli studi, superiore al placebo nel migliorare molti parametri clinici in tutti gli studi, e si differenzia maggiormente dal placebo rispetto agli inibitori selettivi della ricaptazione della serotonina. Il suo profilo di effetti collaterali è solo lievemente sfavorevole rispetto al placebo e il suo tasso di drop-out è leggermente superiore a quello del placebo. La duloxetina è efficace nei pazienti anziani anche su alcune sintomatologie dolorose organiche in comorbidità con la sintomatologia depressiva. **Conclusioni.** L'efficacia e la tollerabilità della duloxetina nel paziente anziano con DDM sono simili a quelle riscontrate nel paziente adulto. Vi è una relativa scarsità di studi comparativi, eccetto che contro placebo. I peculiari bisogni e aspetti clinici dei pazienti anziani con DDM vanno affrontati con attente e costanti visite, per evitare errori nella prescrizione dei dosaggi dei farmaci.

**PAROLE CHIAVE:** duloxetina, disturbo depressivo maggiore, dolore, anziano, farmacoterapia antidepressiva.

## INTRODUCTION

Major depressive disorder (MDD) is common in aged people and is frequently associated with cognitive impairment and disability. Furthermore, clinically significant depressions, like MDD and other forms of unipolar depression constitute part of the clinical course of dementia in the elderly, or complicate it or are frequently comorbid with it.

MDD affects about 1-4% of the general aged population (1), accounting for almost 5% of dementia syndromes (2). Kobayashi (3) introduced a new and more dynamic approach to investigate the relationship between depression and dementia, coining the term of "depression-dementia medius". Within this model, depression, cognitive impairment, and degenerative dementia are viewed as an intersecting *continuum*, in which pseudodementia and depression in dementia are located intermediately between depression and dementia.

Apathy is characterized by a partial lack of motivation, but differently from avolition, it also concerns a sluggish response to environmental stimuli, a sort of emotional unresponsiveness. It is primary deficit that should be distinguished from both cognitive decline and depressive mood. Apathy may be a common feature of psychotic disorders, it may be part of a depressive syndrome, and may be extremely common in dementia. It coexists with depression in the same patient all too frequently, but it should be routinely assessed during neuropsychiatric evaluation independently from depression. In distinguishing the two syndromes, symptoms of sadness and feelings of helplessness, hopelessness, and worthlessness are helpful in attributing the case to depression. Accurately differentiating apathy from depression is basic to achieve appropriate family education, thus allowing the institution of the best indicated treatment strategy (4).

Another important aspect in elderly patients with MDD is the partial androgen deficiency of aging men (PADAM). It results in a variety of behavioral symptoms, like weakness and increased fatigability, depressive mood, lack of motivation, low energy, reduced performance at job and sports, reduced vitality, increased anxiety and irritability, insomnia, difficulty in concentrating, and impaired memory. Decreased libido and low dominance may reflect reduced testosterone levels; in fact, the syndrome may be reversed through exogenous testosterone supply (5-7). Psychological and behavioral aspects of PADAM overlap with signs and symptoms of MDD. The evidence of the association between low testosterone (T) levels and depressive mood in men stems from studies assessing depression in people with hypogonadism, and reporting the posi-

tive effects of androgen replacement on mood. The role of androgens in the human involves both the regulation of sexuality and psychological aspects like aggression, social ranking, general emotionality, and personality. These effects are also influenced by social factors. Besides this, sex hormones play a cardinal role in the development and maintenance of acquired cognitive abilities. At least in part, hormonal changes in androgen levels in elderly men modulate cognitive changes occurring with aging. Treatment with androgens in hypogonadal men improved neurocognition and mentation, verbal and visual memory, visuomotor scanning and attention, verbal fluency and understanding, and spatial abilities and memory for both verbal and visual information. The behavioral symptoms of PADAM may be ascribed to multiple factors, including both biological changes occurring with age and social adaptations occurring during the mid-life transition (5,6).

Similar considerations may be made for postmenopausal women, a group of persons in which depressive and sexual symptoms are more severe than in other age groups and are both associated with stressful life events (8,9). Postmenopausal women with MDD showed better antidepressant response to selective serotonin reuptake inhibitors (SSRIs) when this treatment has been administered in combination with hormonal substitution therapy (10).

Another important point in elderly depression is the increased risk of suicide. Various combinations of risk factors for suicide must be considered in the elderly. The concomitance of depressive symptoms and stressful life events, such as feelings of loss, loneliness, and physical illness in the elderly are to be considered as warning signs for suicidal behavior (11,12). Loss of libido and other aspects of sexuality may also constitute a significant part of suicidal ideation in the elderly (13).

The physician should carefully assess, for elderly patients with depression, any underlying organic causes and comorbidities, including diabetes (14,15), hypertension (16), cardiovascular diseases (17), obesity (18,19), deficiency of vitamin B12 (20,21), vitamin D (22,23), folate (20,24,25), homocysteine (20,25,26), anemia or iron deficiency (27,28) or iron overload (29-32), and in general, the state of nutrients and micronutrients that might influence mood (33).

Duloxetine inhibits the transporters of both serotonin (5-HT) and norepinephrine (NA), thus it belongs to the class of the Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs). A meta-analysis conducted by Girardi et al. (34) showed that duloxetine has good evidence of efficacy in acute, adult MDD, especially at doses of 80-120 mg/day. About six hours after oral administration, duloxetine reaches a maximum plasma

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concentration ( $C_{max}$ ) of approximately 47 ng/mL with 40 mg twice-daily dosing, to 110 ng/mL with 80 mg twice-daily dosing. Its elimination half-life is approximately 10-12 hours, while its distribution volume is about 1640 L. Gender, smoking, age, ethnicity, cytochrome P450 (CYP) 2D6 genotype, liver and renal function were all found to influence its pharmacokinetics. Of these, only impaired liver or renal function prompted specific warnings or recommendations for dose adjustment. Drug-drug interaction studies showed activated charcoal and CYP1A2 inhibition to significantly decrease and increase, respectively, plasma levels of duloxetine. For example, fluvoxamine, an SSRI and CYP1A2 and CYP2D6 inhibitor, increased the area under the curve of duloxetine by 460% and its  $C_{max}$  by 141%. Most of the effect is due to CYP1A2 inhibition, with CYP2D6 contributing much less. In contrast, smoking decreases duloxetine plasma concentrations by 30%. The CYP2D6 poor metabolizer status or concomitant administration of CYP2D6 inhibitors does not require dose adjustment. Duloxetine increases the exposure to drugs metabolized by CYP2D6, but not by CYP1A2. Furthermore, duloxetine may enhance the effects of benzodiazepines, but not those of alcohol or warfarin (35). Its concentration in human plasma can be determined by capillary electrophoresis with laser-induced fluorescence detection (36), or by liquid chromatography (37); these techniques proved to be reliable for determining the plasma levels of other antidepressants (38,39) and antipsychotic drugs (40).

The aim of this paper is to briefly review the main evidence about the treatment with duloxetine of elderly people with depression.

### **METHOD**

From the 3<sup>rd</sup> to the 7<sup>th</sup> of September, current year, we searched the Medline, Embase, and PsycLIT databases using as terms “duloxetine”, “elderly”, “depression”, “aging” or “ageing”, “aged”, “major depression”, “major depressive disorder”, and “major depressive episode”. Papers were included if they satisfied standards for adequate methodology and population included and had focused on the subject. Exclusion criteria comprised inadequate methodology (method unspecified and/or inadequately described), not reporting data of treatment efficacy or side effects, and unspecified inclusion of subjects.

Papers published in peer-reviewed journals dealing with duloxetine treatment in elderly people were selected. Almost all of these were published in the last 10 years. Further papers that did not appear in the above databases were searched from reference lists of retrieved papers.

### **RESULTS**

The combined search yielded 212 papers as of September the 7<sup>th</sup>, 2012, of which 8 were highly specific (keywords appearing in paper title), 11 were most relevant, while 128 were of some relevance. Three of the highly relevant papers were reviews or metaanalyses and the other eight were clinical trials. We briefly discuss their findings.

### **DISCUSSION**

#### *Effectiveness*

Duloxetine significantly improved the mean baseline HAM-D-17 total score of elderly patients with depression (41,42). A summary of the results of studies using duloxetine in elderly populations is shown in **Table 1**.

In previous short-term studies, the comparisons between duloxetine and placebo of HAM-D-17 subscores showed differences favoring duloxetine, which were significant in some items (core, retardation, Maier subscores) or at the limit of the level of significance in anxiety (strong trend, as in the study conducted by Nelson and colleagues) (43). By the 2<sup>nd</sup> week of treatment, a short-term placebo-controlled study focusing on elderly patients showed significant benefits over placebo in Geriatric Depression Scale (GDS) total score and CGI-S, and significantly greater reduction than placebo in psychic anxiety and in the anxiety somatization subscales (44). In a recent randomized, double-blind, placebo-controlled trial, duloxetine was used as a comparator in a fixed-dose study investigating the efficacy and safety of Lu AA21004 in elderly patients with MDD (45). In this sponsored trial, signed by one single principal investigator and two sponsoring pharmaceutical company employees, both drugs showed superiority to placebo at weeks 6 and 8. However, duloxetine ranked better than the experimental drug on all clinical measures, but the analysis model used avoided the direct comparison of the two drugs (45).

Another comparison with placebo showed that duloxetine has a shorter time to antidepressant response (46). Additional analysis showed that the effect of duloxetine on depression and quality of life was not significantly affected by the presence of comorbid vascular disease, diabetes, arthritis or a combination of more than one of the above (41,47).

Regarding anxiety, another study conducted by Davidson and colleagues (48), who pooled acute-phase data from a subset of patients ( $\geq 65$  years) with

**Table 1. Summary of studies of duloxetine in elderly populations with major depressive disorder**

Study	Patients	Study design	Primary efficacy measures	Secondary efficacy measures	Main results
Wohlreich et al. (51)	Patients with MDD (DSM-IV) Age ≥65 years N=101	Multinational, open-label study 52 weeks Duloxetine Dosage 80-120 mg	HAMD17 total score	CGI-S HAMD17 subscales BDI-II PGI-I SDS	Mean changes in HAMD17 total score at Weeks 6, 28, and 52 were -13.0, -17.4 and -17.5 (all p-values <.001). Significant improvement (p<.001) in CGI-S and PGI-I at Week 1 and sustained throughout the study. Response rates at Weeks 6, 28, and 52: 62.9%, 84.9%, and 89.4%, respectively; Rates of remission were 41.4%, 69.8%, and 72.3%, respectively. Adverse events led to discontinuation in 27 (26.7%) patients. Treatment-emergent adverse events reported by >10% of patients included dizziness, nausea, constipation, somnolence, insomnia, dry mouth, and diarrhea. Most events occurred early in the study. Mean changes at endpoint in blood pressure and body weight were less than 2.0 mm Hg, and -0.1 kg, respectively.
Nelson et al. (43)	Patients with MDD (DSM-IV) Age ≥55 N=90	Two identical, multicenter, double-blind studies in which patients with MDD were randomized to receive placebo (N=43) or duloxetine (60 mg/day; N=47) for 9 weeks	HAMD17 total score	VAS	Duloxetine resulted significantly superior to placebo for mean change in HAMD17 total score. Estimated remission for duloxetine-treated patients (44.1%) was significantly higher than that for placebo (16.1%). Reductions in overall pain, back pain, and pain while awake were also significantly greater for duloxetine than placebo. The rate of discontinuation due to adverse events was significantly higher for duloxetine-treated patients (21.0%) than placebo (6.7%). Abnormal elevations in vital signs at endpoint were not significantly different from placebo.
Raskin et al. (44)	Patients with MDD (DSM-IV) Age: 65-89 N=311	Multicentre, randomised, double-blind, placebo-controlled study: 1-week screening phase; 1-week, double-blind, placebo 8-weeks duloxetine 60 mg/day (n=207) or placebo (n=104) 1-week, double-blind, discontinuation phase in which the dosage of duloxetine was tapered to 30 mg/day for 4 days.	VLRT SDST 2DCT LNST	GDS HAMD17 CGI-S VAS SF-36	As compared to placebo, Duloxetine improved the composite cognitive score, GDS and HAMD17 total scores, CGI-Severity, HAMD17 response and remission rates. Duloxetine significantly improved Visual Analogue Scale scores for back pain and time in pain while awake versus placebo. Significantly fewer patients withdrew from the study because of lack of efficacy (2.9% versus 9.6%); the incidences of discontinuation due to adverse events were similar for duloxetine and placebo (9.7% versus 8.7%)
Russell et al. (49)	Patients with MDD (DSM-IV) Age: ≥65 N=311	<i>Post-hoc</i> analyses of a multicenter, parallel, double-blind, placebo-controlled study by Raskin et al., 2007 Psychic Anxiety item, Somatic Anxiety item, and Anxiety-Somatization subscale from HAMD17	Psychic Anxiety item, Somatic Anxiety item, and Anxiety-Somatization subscale from HAMD17	GDS VAS VLRT SDST 2DCT LNST	Duloxetine vs. Placebo significantly reduced Psychic Anxiety (least-squares mean change: -0.62 vs. -0.18, p<0.001) and Anxiety/Somatization subscale (-1.88 vs. -0.99, p=0.002). Significant improvement occurred in the <75 and ≥75 age groups for Psychic Anxiety, but only in the <75 group for the Anxiety/Somatization subscale. Duloxetine-treated patients with high anxiety showed significant improvement compared with placebo-treated patients on Psychic Anxiety, Anxiety/Somatization subscale, the HAMD17 total score, and several other measures. Duloxetine and placebo had similar discontinuation due to adverse events.
Wise et al. (64)	Patients with MDD (DSM-IV) Age: ≥65 N=311	<i>Post-hoc</i> analyses of a multicenter, parallel, double-blind, placebo-controlled study by Raskin et al., 2007	VLRT SDST 2DCT LNST	GDS HAMD17 CGI-S VAS SF-36	Duloxetine vs. Placebo proved significantly greater efficacy for the composite cognitive score, GDS and HAMD17 total scores, CGI-S, HAMD17 response and remission rates, and some of the SF-36 and VAS measures. Few treatment-by-comorbidity subgroup interactions for efficacy variables or for adverse events reported as the reason for discontinuation and common treatment emergent adverse events. The efficacy of duloxetine on cognition and depression in elderly patients, and its tolerability, were not largely affected by the comorbidity status.

Continue

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**Continue Table 1.**

Study	Patients	Study design	Primary efficacy measures	Secondary efficacy measures	Main results
Karp et al. (52)	Patients with MDD (DSM-IV) Age: ≥65 N=274 HAM-D-17 score ≥15, MMSE score ≥18	Data analysis of 40 patients switched from escitalopram to duloxetine Data up to 16.5 weeks	HAMD17 total score	HRSA MMSE UKU CIRS-G MOS	50% patients met criteria for full response, 17.6% were partial responders and 32.5% did not respond. The median time to response was 12 weeks. 17, 85% responders were females, whereas responders and non-responders did not differ in terms of age, marital status, education, recurrent depression, age on onset of the first depressive episode
Raskin et al. (61)	Patients with MDD (DSM-IV) Age: ≥65 N=311	Post-hoc analyses of a multicenter, parallel, double-blind, placebo-controlled study by Raskin et al., 2007	GDS HAMD17 CGI-S VAS	The time to response and remission for duloxetine compared with placebo was evaluated using Cox proportional hazards (PH) modeling, Kaplan-Meier estimation, and categorical repeated measures analysis	Discontinuation rates due to adverse events were similar for duloxetine and placebo (9.7% vs 8.7%). Treatment-emergent dry mouth, nausea, and diarrhea occurred significantly ( $p \leq 0.05$ ) more frequently with duloxetine. Changes in supine and standing blood pressure, in sustained elevation in BP and treatment-emergent orthostatic hypotension, in pulse and in corrected QT (QTc) interval were not significantly different between duloxetine and placebo, except for change in orthostatic systolic BP (-2.45 vs 0.93 mmHg; $p = .017$ ). The duloxetine group showed significant weight loss compared with the placebo group (-0.73 kg vs -0.13 kg; $p = 0.009$ ). Of 5 hepatic analytes, the only significant difference was an increase in alkaline phosphatase in duloxetine compared with placebo ( $p = 0.017$ ); this difference was not considered clinically relevant. The incidence of 1 or more discontinuation-emergent adverse events was not significantly different between the duloxetine and placebo groups (17.3% vs 11.3%).
Katona et al. (45)	Patients with MDD (DSM-IV-TR) Age: ≥65 N=452 MMSE ≥24 Montgomery-Åsberg Depression Rating Scale (MADRS) ≥26	Multicenter, 8-week, 1:1:1 randomized, placebo-controlled, double-blind trial vs. Lu AA21004  Duloxetine 60 mg/day vs. Lu AA21004 5 mg/day or placebo	HAMD24 total score at week 8 with analysis of covariance with last observation carried forward and with mixed model for repeated measures	Response and remission; HAMD24 at all points; Montgomery-Åsberg Depression Rating Scale scores; CGI-S scores; Rey Auditory Verbal Learning Test; Digit Symbol Substitution Test	Duloxetine and Lu AA21004 showed significantly greater improvement vs placebo at weeks 6 and 8. Covariance and mixed-model effects converged. Lu AA21004, but not duloxetine, positively affected cognition. According to the HAMD, 8-week response was found in 35.2% of patients receiving placebo, 53.2% of patients receiving Lu AA21004, and in 63.3% of patients receiving duloxetine, while remitters were respectively 19.3%, 29.2%, and 34.7%. Lu AA21004 differed for one adverse event from placebo, while duloxetine differed for six.
Robinson et al. (50)	Patients with MDD (DSM-IV) Age: ≥65 N=279 MMSE ≥20 Montgomery-Åsberg Depression Rating Scale ≥20	Multicenter, 24-week (12-week short-term and 12-week continuation), randomized, placebo-controlled, double-blind trial Duloxetine 60 or 120 mg/day or placebo; placebo rescue possible	HAMD17 total score	GDS BPI NRS CGI-S PGI-I cognitive measures	Duloxetine vs placebo showed significantly greater improvement at weeks 4, 8, 16, and 20. Similar patterns for Geriatric Depression Scale and Clinical Global Impression-Severity scale emerged, with significance also seen at week 24. There was a significant treatment effect for all BPI items and 4 of 6 NRS pain measures in the acute phase, most BPI items and half of the NRS measures in the continuation phase. More duloxetine-treated patients completed the study (63% versus 55%). A significantly higher percentage of duloxetine-treated patients versus placebo discontinued due to adverse event (15.3% versus 5.8%)
<p><i>Legend:</i> <b>2DCT:</b> 2 Digit Cancellation Test; <b>BDI-II:</b> Beck Depression Inventory-II; <b>BPI:</b> Brief Pain Inventory; <b>CGI-S:</b> Clinical Global Impression of Severity scale; <b>DSM-IV:</b> Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; <b>GDS:</b> Geriatric Depression Scale; <b>CIRS-G:</b> Cumulative Illness Rating Scale for Geriatrics; <b>HAMD17:</b> 17-item Hamilton Rating Scale for Depression; <b>HRSA:</b> Hamilton Rating Scale for Anxiety; <b>LNST:</b> Letter-Number Sequencing Test; <b>MDD:</b> Major Depressive Disorder; <b>MMSE:</b> Mini-Mental State Examination; <b>MOS:</b> Medical Outcomes Study; <b>NRS:</b> Numeric Rating Scales for pain; <b>PGI-I:</b> Patient Global Impression of Improvement scale; <b>SDS:</b> Sheehan Disability Scale; <b>SDST:</b> Symbol Digit Substitution Test; <b>SF-36:</b> 36-Item Short Form Health Survey; <b>UKU:</b> Udvalg for Kliniske Undersogelser-Committee of Clinical Investigations Side Effect Rating Scale; <b>VAS:</b> Visual Analogue Scale for pain; <b>VLRT:</b> Verbal Learning and Recall Test.</p>					

generalized anxiety disorder (GAD) from four randomized, double-blind, placebo-controlled trials of duloxetine (three using flexible dosing and one using fixed doses), showed duloxetine 60-120 mg once daily for 9-10 weeks to be efficacious and tolerable in elderly patients with generalized anxiety disorder, as compared to placebo. It should be remarked that GAD is a disorder with much symptomatological overlap with depressive mood disorders which responds in a similar manner to antidepressant drugs.

Briefly, short-term studies indicate that duloxetine treatment in aged people with depression improves depressive symptoms, as assessed through the total score on the 17-item HAM-D. Furthermore, it reduces generalized, psychic, and somatization anxiety (43,48, 49). Duloxetine is faster than placebo to show antidepressant response and is also effective when there are comorbid vascular diseases, diabetes, arthritis or more than one of these.

In a recent multicenter, multinational, 24-week (12-week short-term and 12-week continuation), randomized, placebo-controlled, double-blind trial carried-out by Robinson et al. (50), patients who received duloxetine showed significantly greater improvement on the Hamilton's Maier subscale at weeks 4, 8, 16, and 20. Furthermore, duloxetine-receiving patients had significantly lower pain ratings during both the acute and the continuation phases, but dropped-out three times as much as their placebo-receiving counterparts.

Long-term data showed that duloxetine maintains its efficacy over time; HAM-D-17 total score and all subscales significantly improved up to the 52<sup>nd</sup> week (51). CGI-S improvement in elderly patients paralleled that of the remaining included population of non-elderly adults.

Another long-term study showed that 50% of patients who switched from escitalopram to duloxetine met criteria for full response, 17.6% of them were partial responders and 32.5% did not respond (52). The median time to response was 12 weeks. Female gender was associated with a higher probability of response, whereas other measures, like history of depression and baseline MMSE scores did not affect the rate of response. Psychological and somatic anxiety improved over time following treatment with duloxetine (52). The improvement of depressive symptoms with duloxetine was dissimilar to improvements obtained with placebo, while escitalopram induced changes that looked like those of placebo-treated patients (53).

Duloxetine proved to be effective also in pain relief and urinary incontinence (54). In a short-term, placebo-controlled study, patients experienced rapid pain

relief, and the comparison versus placebo showed statistically significant differences in scores on the visual analogue scale (VAS) pain ratings, in back pain, and in the amount of pain experienced while awake (55). Furthermore, patients showed faster improvement in self-reported pain compared to placebo (56). Moreover, duloxetine produced significant reduction in overall pain severity, back pain, time in pain while awake, and interference with daily activities in patients with depression and comorbid arthritis (57). Briefly, the beneficial effects of duloxetine on pain were statistically significant and clinically meaningful, extending from the acute to the continuation phase, thus prompting to hypothesize that they are not subjected to tolerance with time (50).

In an eight-week, placebo-controlled study (44), treatment with duloxetine ensued in significant improvement, compared to placebo, on the composite measure of cognitive functions; duloxetine proved to be the most important determinant of the improvement driven by verbal learning and memory; on the other hand, measures of focused attention and executive functioning showed no significant differences between duloxetine and placebo.

Duloxetine was found to be effective in patients with urinary stress incontinence (54); however, it may be associated with a decline in urinary flow in elderly men (55). At any rate, duloxetine is a safe and effective treatment for elderly women with symptoms of stress urinary incontinence or stress-predominant mixed urinary incontinence (56), with elderly women with urinary incontinence showing a safety profile for duloxetine which was comparable to that of their younger counterparts (57). Duloxetine is also effective in other pathological conditions of the aged, including fibromyalgia (58), osteoarthritis (47,59), and diabetic sensory polyneuropathy (60).

#### *Effects on physiological functions*

The changes from baseline of heart rate and standing and supine blood pressure, sustained hypertension and the number of patients with abnormal changes did not differ significantly between the duloxetine- and placebo-treated patients (44,61). The rate of treatment-emergent orthostatic hypotension, defined as standing diastolic blood pressure (BP) at least 10 mmHg less than supine diastolic BP and standing systolic BP at least 20 mmHg than supine systolic BP, was numerically higher in the placebo group compared to the duloxetine group, though this did not reach statistical significance. Using an orthostatic change of 10 mmHg for both systolic and dias-

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tolic BP, the rates of treatment-emergent orthostatic hypotension were similar and not significantly different between duloxetine- and placebo-treated patients, for both diastolic and systolic BP. No significant differences in mean changes of QTc interval has been detected between duloxetine- and placebo-treated patients, independently from whether the Bazett or the Fridericia formulas were used (61). In the analysis at the one-year follow-up, duloxetine-treated patients exhibited small and nonsignificant decreases in blood pressure and increases in heart rate from baseline to end point (51). Patients with higher baseline BP values had comparatively greater BP lowering effects, as compared with normotensive individual. Duloxetine did not appear to prolong the QTc interval in the elderly, and this is consistent with what has already been published for nonelderly patients and healthy volunteers (62,63).

Treatment with duloxetine was associated with a small (<1 kg) decrease in weight in the short-term. However, mean body weight slightly increased after one year, whereas the rate of patients with significant weight gain was not less than that of patients with significant weight decrease (41). Considered cumulatively, these data do not clarify whether duloxetine increases or decreases body weight; the drug apparently affects body weight, albeit in an unpredictable direction.

In the short-term comparative analysis, no significant differences between duloxetine and placebo emerged concerning the incidence of abnormal laboratory values (hematology and blood chemistry). Long-term data did not show clinically significant abnormalities (41).

Duloxetine did not affect sexual function differently from placebo in elderly people, as assessed with the Arizona Sexual Experience Scale (43). This is important, as the presence of sexual alterations are not to be considered a minor point in such populations, given their possible repercussions on self-esteem and the consequent influence on suicidal behavior (13).

#### *Adverse events*

Although the rate of discontinuation due to adverse events in the short-term pooled data (61) was higher in patients receiving duloxetine than in those on placebo, direct head-to-head comparisons did not show any difference in the entire patient sample (9.7% vs 8.7%; NS), even when the sample was dichotomized in a <75-year-old and a ≥75-year-old subgroup (44,61). Rates of dry mouth, nausea and diarrhea were significantly higher in patients receiving duloxetine, as compared to patients receiving placebo. Nausea and fatigue showed

significant heterogeneity when data were analyzed according to an age-related stratification (<75 years-old and ≥75 years-old). In the <75 subgroup, nausea was significantly more frequent in duloxetine-treated patients, whereas in the ≥75 subgroup, nausea was more frequent in the placebo subgroup. Fatigue was significantly more frequent for duloxetine-treated patients in the ≥75 subgroup (61). There was a statistically significant greater mean decrease in weight for patients treated with duloxetine versus patients treated with placebo (-0.73 vs -0.13 kg; p=0.009) (39). *Post hoc* analyses of this study also showed duloxetine to be very well tolerated in patients with medical comorbidities (64). Dry mouth and gastrointestinal complaints were the adverse events that were significantly more common with duloxetine than with placebo in the short-term direct comparison (44), irrespective of the occurrence of comorbidities (64). Other types of adverse events (e.g., insomnia, fatigue, diminished appetite, and reduced libido) in the pooled short-term data (43) were seen significantly more often in patients receiving duloxetine, as compared with those receiving placebo.

Long-term observation showed that most adverse events occurred early in the study and were of mild or moderate intensity (51). The rates of events in patients aged ≥65 years were not significantly higher than in the 18-64 year age range in the same study. In the comparison between age ranges, patients aged ≥65 years reported a significantly lower incidence of insomnia and headache than younger patients, while no significant differences between age cohorts were found in the analysis of all other side effects.

Five (12.5%) patients who switched from escitalopram to duloxetine (52) discontinued the study due to adverse events. In the analysis of total and subscale scores of the Udvalg Kliniske Undersøgelser (UKU) scale (65), there were small but statistically significant decreases (i.e., improvements) in somatic complaints (as reflected by the total UKU scores), on the psychological subscale and other systems subscale scores.

Considering the lack of evidence concerning suicidal risk in elderly patients with depression receiving duloxetine, a careful assessment of suicide risk is essential in this category of patients.

The literature reports the following common side effects associated with duloxetine overdose: nausea, headache, dry mouth, fatigue, insomnia, dizziness, somnolence, constipation, considerable increases in recumbent systolic and diastolic blood pressure, and a small decrease in heart rate (66,67). A review of the annual reports of the American Association of Poison Control Centers (AAPCC) shows that there has been an in-

**Table 2. Summary of the effects (and the lack of them) of the use of duloxetine in elderly patients**

Psychological symptom improvement	Somatic symptom improvement	Possible side effects	Overdose symptoms	Advantages
Depression Psychic anxiety Somatization anxiety Generalized anxiety	Vascular disease* Diabetes* Arthritis* Low-back pain* Urinary stress incontinence in women Fibromyalgia Osteoarthritis Diabetic sensory polyneuropathy	Dry mouth Nausea Diarrhoea Decreased appetite Insomnia Fatigue Decreased libido Decline in urinary flow in men Small short-term weight decrease (<1 kg) Slight weight increase at one year	Nausea Headache Dry mouth Fatigue Insomnia Dizziness Somnolence Constipation Considerable increases in recumbent systolic and diastolic blood pressure Small decrease in heart rate Complication of thromboembolism	No effect on heart rate No changes in standing blood pressure No changes in supine blood pressure No current evidence of QTc prolongation Pain relief No changes in haematological measures and blood chemistry Few effects on sexual function Well-tolerated in patients with organic comorbidities

\*with comorbid depression/anxiety.

crease in fatal cases in which duloxetine has been identified: 5 cases in 2005 (68), 11 cases in 2006 (69), 14 cases in 2007 (70), 18 cases in 2008 (71), 23 cases in 2009 (72), and 12 in 2010 (73). “Cocktail” drugs caused most of the poisonings; only a few cases of poisoning were due to duloxetine alone, which somehow has been linked to pulmonary embolism (74). However, this apparent increase in duloxetine mortality in the US should be viewed against the background of the increased use of the drug across the year, hence the above figures were to be expected and are by no means excessive with respect to other similar drugs. The recent decrease in duloxetine-associated mortality is to be interpreted as the result of preventive policies and campaigns carried-out by the US health administration.

The ingestion of high quantities of duloxetine may have serious outcomes such as complicating thromboembolism (75). Elderly patients who are taking duloxetine should be advised to avoid overdosage, which in most cases may be attributed to careless ingestion by cognitively impaired individuals with depression. Patients should be prompted to rely on family members for the control of their medication intake and encouraged to promptly contact their physician in cases of inadvertent drug ingestion, so to institute timely detoxifying strategies and interventions. A summary of the strength and weaknesses of duloxetine use in the aged is shown in **Table 2**.

## CONCLUSIONS

Duloxetine is effective, safe and well-tolerated in elderly populations with depressive disorders in a sim-

ilar manner to adults. Its’ efficacy is similar to that of other antidepressants, like the SSRIs or other SNRIs, like venlafaxine and milnacipran, although regrettably, comparisons in elderly populations are lacking. It might have some advantage with respect to SSRIs, in terms of dissimilarity with respect to placebo. However, there is a relative lack of studies of duloxetine in aged patients with depressive disorders. Elderly patients with dementia or pseudodementia must be closely followed to avoid inappropriate dosing, as this may expose patients to life-threatening effects.

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