

Duloxetine in the treatment of elderly people with major depressive disorder

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

ANTONIO DEL CASALE¹, PAOLO GIRARDI^{1,2}, ROBERTO BRUGNOLI¹, GABRIELE SANI¹,
SIMONE DI PIETRO¹, CHIARA BRUGNOLI¹, FEDERICA CACCIA¹, GLORIA ANGELETTI¹,
DANIELE SERATA^{1,2}, CHIARA RAPINESI^{1,2}, ROBERTO TATARELLI¹, GEORGIOS D. KOTZALIDIS¹
E-mail: antonio.delcasale@uniroma1.it

¹School of Medicine and Psychology, NESMOS Department (Neuroscience, Mental Health and Sensory Organs), Sant'Andrea Hospital, Sapienza University of Rome, Italy

²Department of Neuropsychiatry, Villa Rosa Hospital, Suore Ospedaliere del Sacro Cuore di Gesù, Viterbo, Italy

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 comorbilità 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

Duloxetine in the treatment of elderly people with major depressive disorder

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 3rd to the 7th 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 7th, 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 2nd 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 (≥ 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

Duloxetine in the treatment of elderly people with major depressive disorder

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%)

Legend: 2DCT: 2 Digit Cancellation Test; BDI-II: Beck Depression Inventory-II; BPI: Brief Pain Inventory; CGI-S: Clinical Global Impression of Severity scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; GDS: Geriatric Depression Scale; CIRS-G: Cumulative Illness Rating Scale for Geriatrics; HAMD17: 17-item Hamilton Rating Scale for Depression; HRSA: Hamilton Rating Scale for Anxiety; LNST: Letter-Number Sequencing Test; MDD: Major Depressive Disorder; MMSE: Mini-Mental State Examination; MOS: Medical Outcomes Study; NRS: Numeric Rating Scales for pain; PGI-I: Patient Global Impression of Improvement scale; SDS: Sheehan Disability Scale; SDST: Symbol Digit Substitution Test; SF-36: 36-Item Short Form Health Survey; UKU: Udvalg for Kliniske Undersogelser-Committee of Clinical Investigations Side Effect Rating Scale; VAS: Visual Analogue Scale for pain; VLRT: Verbal Learning and Recall Test.

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 52nd 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-

Duloxetine in the treatment of elderly people with major depressive disorder

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.

Acknowledgements. We are grateful to Ms. Mimma Ariano, the late Tiziana Mattei, and Ms. Felicia Proietti, Librarians of the Sant’ Andrea Hospital, School of Medicine and Psychology, Sapienza University of Rome, for allowing us to access precious bibliographical material. We also thank Ms. Lucilla Martinelli for skillful assistance in the preparation of this manuscript.

Financial & Competing Interests Disclosure. In the past two years, Paolo Girardi has received research support from Lilly, Janssen, and Springer Healthcare, and has participated in Advisory Boards for Lilly, Otsuka, Pfizer, Schering, and Springer Healthcare and received honoraria from Lilly and Springer Healthcare. All other authors of this paper have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

This work has not been supported by any funding.

REFERENCES

- Blazer DG. Depression in late life: review and commentary. *Gerontol A Biol Sci Med Sci* 2003; 58: 249-65.

Duloxetine in the treatment of elderly people with major depressive disorder

2. Clarfield AM. The reversible dementias: do they reverse? *Ann Intern Med* 1988; 109: 476-86.
3. Kobayashi T, Kato S. Depression-dementia medius: between depression and the manifestation of dementia symptoms. *Psychogeriatrics* 2011; 11: 177-82.
4. Tagariello P, Girardi P, Amore M. Depression and apathy in dementia: same syndrome or different constructs? A critical review. *Arch Gerontol Geriatr* 2009; 49: 246-9.
5. Amore M. Partial androgen deficiency and neuropsychiatric symptoms in aging men. *J Endocrinol Invest* 2005; 28 (11 suppl proceedings): 49-54.
6. Amore M, Scarlatti F, Quarta AL, Tagariello P. Partial androgen deficiency, depression and testosterone treatment in aging men. *Aging Clin Exp Res* 2009; 21: 1-8.
7. Amore M, Innamorati M, Costi S, Sher L, Girardi P, Pompili M. Partial androgen deficiency, depression, and testosterone supplementation in aging men. *Int J Endocrinol* 2012; 2012: 280724.
8. Amore M, Di Donato P, Berti A, et al. Sexual and psychological symptoms in the climacteric years. *Maturitas* 2007; 56: 303-11.
9. Dennerstein L, Soares CN. The unique challenges of managing depression in mid-life women. *World Psychiatry* 2008; 7: 137-42.
10. Zanardi R, Rossini D, Magri L, Malaguti A, Colombo C, Smeraldi E. Response to SSRIs and role of the hormonal therapy in post-menopausal depression. *Eur Neuropsychopharmacol* 2007; 17: 400-5.
11. Pompili M, Innamorati M, Masotti V, et al. Suicide in the elderly: a psychological autopsy study in a North Italy area (1994-2004). *Am J Geriatr Psychiatry* 2008; 727-35.
12. Innamorati M, Tamburello A, Lester D, et al. Inequalities in suicide rates in the European Union's elderly: trends and impact of macro-socioeconomic factors between 1980 and 2006. *Can J Psychiatry* 2010; 55: 229-38.
13. Klug A, Lindner R, Fiedler G, Altenhöfer A. Sexualität suizidaler Älterer. *Z Gerontol Geriatr* 2008; 41: 22-8.
14. Albers B, Kruse J, Giani G, Icks A. Diabetes and incident depression: Is the association mediated or modified by sociodemographic factors or co-morbidities? A systematic review. *Exp Clin Endocrinol Diabetes* 2011; 119: 591-8.
15. Dziemidok P, Makara-Studziska M, Jarosz MJ. Diabetes and depression: a combination of civilization and life-style diseases is more than simple problem adding. Literature review. *Ann Agric Environ Med* 2011; 18: 318-22.
16. García-Fabela L, Melano-Carranza E, Aguilar-Navarro S, García-Lara JM, Gutiérrez-Robledo LM, Avila-Funes JA. Hypertension as a risk factor for developing depressive symptoms among community-dwelling elders. *Rev Invest Clin* 2009; 61: 274-80.
17. Saran RK, Puri A, Agarwal M. Depression and the heart. *Indian Heart J* 2012; 64: 397-401.
18. Apostolopoulou M, Savopoulos C, Michalakis K, Coppack S, Dardavessis T, Hatziolios A. Age, weight and obesity. *Maturitas* 2012; 71: 115-9.
19. Han TS, Tajar A, Lean ME. Obesity and weight management in the elderly. *Br Med Bull* 2011; 97: 169-96.
20. Stanger O, Fowler B, Piertz K, et al. Homocysteine, folate and vitamin B12 in neuropsychiatric diseases: review and treatment recommendations. *Expert Rev Neurother* 2009; 9: 1393-412.
21. Wolters M, Ströhle A, Hahn A. Cobalamin: a critical vitamin in the elderly. *Prev Med* 2004; 39: 1256-66.
22. Annweiler C, Souberbielle JC, Schott AM, de Decker L, Berrut G, Beauchet O. Vitamine D chez la personne âgée: les 5 points à retenir. *Geriatr Psychol Neuropsychiatr Vieil* 2011; 9: 259-67.
23. Parker G, Brotchie H. "D" for depression: any role for vitamin D? "Food for Thought" II. *Acta Psychiatr Scand* 2011; 124: 243-9.
24. Fava M, Mischoulon D. Folate in depression: efficacy, safety, differences in formulations, and clinical issues. *J Clin Psychiatry* 2009; 70 (suppl 5): 12-7.
25. Bottiglieri T. Homocysteine and folate metabolism in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2005; 29: 1103-12.
26. Kuo HK, Sorond FA, Chen JH, Hashmi A, Milberg WP, Lipsitz LA. The role of homocysteine in multisystem age-related problems: a systematic review. *J Gerontol A Biol Sci Med Sci* 2005; 60: 1190-201.
27. Fischbach R, Gastager H, Harrer G. Hyposideremia and endogenous depression. *Pharmakopsychiatr Neuropsychopharmacol* 1973; 6: 252-7.
28. Stewart R, Hirani V. Relationship between depressive symptoms, anemia, and iron status in older residents from a national survey population. *Psychosom Med* 2012; 74: 208-13.
29. Cutler P. Iron overload in psychiatric illness. *Am J Psychiatry* 1991; 148: 147-8.
30. Cutler P. Iron overload and psychiatric illness. *Can J Psychiatry* 1994; 39: 8-11.
31. Feifel D, Young CW. Iron overload among a psychiatric outpatient population. *J Clin Psychiatry* 1997; 58: 74-8.
32. Serata D, Del Casale A, Rapinesi C, et al. Hemochromatosis-induced bipolar disorder: a case report. *Gen Hosp Psychiatry* 2012; 34: 101.e1-3.
33. Kaplan BJ, Crawford SG, Field CJ, Simpson JS. Vitamins, minerals, and mood. *Psychol Bull* 2007; 133: 747-60.
34. Girardi P, Pompili M, Innamorati M, et al. Duloxetine in acute major depression: review of comparisons to placebo and standard antidepressants using dissimilar methods. *Hum Psychopharmacol* 2009; 24: 177-90.
35. Knadler MP, Lobo E, Chappell J, Bergstrom R. Duloxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet* 2011; 50: 281-94.
36. Musenga A, Amore M, Mandrioli R, Kenndler E, de Martino L, Raggi MA. Determination of duloxetine in human plasma by capillary electrophoresis with laser-induced fluorescence detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 2009; 877: 1126-32.
37. Mercolini L, Mandrioli R, Cazzolla R, Amore M, Raggi MA. HPLC analysis of the novel antidepressant duloxetine in human plasma after an original solid-phase extraction procedure. *J Chromatogr B Analyt Technol Biomed Life Sci* 2007; 856: 81-7.
38. Mandrioli R, Mercolini L, Cesta R, Fanali S, Amore M, Raggi MA. Analysis of the second generation antidepressant venlafaxine and its main active metabolite O-desmethylvenlafaxine in human plasma by HPLC with spectrofluorimetric detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 2007; 856: 88-94.
39. Musenga A, Kenndler E, Mercolini L, Amore M, Fanali S, Raggi MA. Determination of sertraline and N-desmethylsertraline in human plasma by CE with LIF detection. *Electrophoresis* 2007; 28: 1823-31.
40. Saracino MA, Amore M, Baioni E, Petio C, Raggi MA. Determination of selected phenothiazines in human plasma by solid-phase extraction and liquid chromatography with coulometric detection. *Analytica Chimica Acta* 2008; 624: 308-16.
41. Mancini M, Gianni W, Rossi A, Amore M. Duloxetine in the management of elderly patients with major depressive disorder: an analysis of published data. *Expert Opin Pharmacother* 2009; 10: 847-60.
42. Tarolla E, Brugnoli R, Pancheri P. Duloxetina: efficacia clinica, sicurezza e tollerabilità nel trattamento del disturbo depressivo maggiore. *Giorn Ital Psicopatol* 2007; 13: 258-78.
43. Nelson JC, Wohlreich MM, Mallinckrodt CH, Detke MJ, Watkin

- JG, Kennedy JS. Duloxetine for the treatment of major depressive disorder in older patients. *Am J Geriatr Psychiatry* 2005; 13: 227-35.
44. Raskin J, Wiltse CG, Siegal A, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry* 2007; 164: 900-9.227-35.
45. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol* 2012; 27: 215-23.
46. Raskin J, Xu JY, Kajdasz DK. Time to response for duloxetine 60 mg once daily versus placebo in elderly patients with major depressive disorder. *Int Psychogeriatr* 2008; 20: 309-27.
47. Wohlreich MM, Sullivan MD, Mallinckrodt CH, et al. Duloxetine for the treatment of recurrent major depressive disorder in elderly patients: treatment outcomes in patients with comorbid arthritis. *Psychosomatics* 2009; 50: 402-12.
48. Davidson J, Allgulander C, Pollack MH, et al. Efficacy and tolerability of duloxetine in elderly patients with generalized anxiety disorder: a pooled analysis of four randomized, double-blind, placebo-controlled studies. *Hum Psychopharmacol* 2008; 23: 519-26.
49. Russell J, Raskin J, Wiltse C, Walker D, Brawman-Mintzer O. Efficacy and tolerability of duloxetine treatment in elderly patients with major depressive disorder and concurrent anxiety symptoms. *Psychiatry (Edgmont)* 2007; 4: 33-45.
50. Robinson M, Oakes TM, Raskin J, Liu P, Shoemaker S, Nelson JC. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. *Am J Geriatr Psychiatry* 2012 Jul 21. Epub ahead of print, doi: 10.1097/JGP. 0b013e31825d08f1.
51. Wohlreich MM, Mallinckrodt CH, Watkin JG, Hay DP. Duloxetine for the long-term treatment of major depressive disorder in patients aged 65 and older: an open-label study. *BMC Geriatr* 2004; 4: 11.
52. Karp JF, Whyte EM, Lenze EJ, et al. Rescue pharmacotherapy with duloxetine for selective serotonin reuptake inhibitor non-responders in late-life depression: outcome and tolerability. *J Clin Psychiatry* 2008; 69: 457-63.
53. Dolder C, Nelson M, Stump A. Pharmacological and clinical profile of newer antidepressants: implications for the treatment of elderly patients. *Drugs Aging* 2010; 27: 625-40.
54. Patel-Gadhia R, Bhal K, Patil P. Retrospective audit on tolerability and efficacy of duloxetine for stress urinary incontinence. *J Obstet Gynaecol* 2011; 31: 258-9.
55. Wade AG, Crawford GM. Urinary flow and urinary symptoms in elderly males exposed to either escitalopram or duloxetine. *Curr Med Res Opin* 2010; 26: 1031-5.
56. Schagen van Leeuwen JH, Lange RR, Jonasson AF, Chen WJ, Viktrup L. Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence. *Maturitas* 2008; 60: 138-47.
57. Skinner MH, Kuan HY, Skerjanec A, et al. Effect of age on the pharmacokinetics of duloxetine in women. *Br J Clin Pharmacol* 2004; 57: 54-61.
58. Cui Z, Zhao Y, Novick D, Faries D. Predictors of duloxetine adherence and persistence in patients with fibromyalgia. *J Pain Res* 2012; 5: 193-201.
59. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. *Age Ageing* 2012; 41: 646-52.
60. Zilliox L, Russell JW. Treatment of diabetic sensory polyneuropathy. *Curr Treat Options Neurol* 2011; 13: 143-59.
61. Raskin J, Wiltse CG, Dinkel JJ, Walker DJ, Desai D, Katona C. Safety and tolerability of duloxetine at 60 mg once daily in elderly patients with major depressive disorder. *J Clin Psychopharmacol* 2008; 28: 32-8.
62. Wernicke J, Lledó A, Raskin J, Kajdasz DK, Wang F. An evaluation of the cardiovascular safety profile of duloxetine: findings from 42 placebo-controlled studies. *Drug Saf* 2007; 30: 437-55.
63. Thase ME, Tran PV, Wiltse C, Pangallo BA, Mallinckrodt C, Detke MJ. Cardiovascular profile of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine. *J Clin Psychopharmacol* 2005; 25: 132-40.
64. Wise TN, Wiltse CG, Iosifescu DV, Sheridan M, Xu JY, Raskin J. The safety and tolerability of duloxetine in depressed elderly patients with and without medical comorbidity. *Int J Clin Pract* 2007; 61: 1283-93.
65. Lingjarde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs, and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychiatr Scand* 1987; Suppl 76: 1-100.
66. Baselt RC. Disposition of toxic drugs and chemicals in man, 8th ed. Foster City (CA) USA: Biomedical Publications, 2008.
67. Sharma A, Goldberg MJ, Cerimele BJ. Pharmacokinetics and safety of duloxetine, a dual-serotonin and norepinephrine reuptake inhibitor. *J Clin Pharmacol* 2000; 40: 161-7.
68. Lai MW, Klein-Schwartz W, Rodgers GC, et al. 2005 Annual Report of the American Association of Poison Control Centers' national poisoning and exposure database. *Clin Toxicol (Phila)* 2006; 44: 803-932.
69. Bronstein AC, Spyker DA, Cantilena LR Jr, Green J, Rumack BH, Heard SE. 2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). *Clin Toxicol (Phila)* 2007; 45: 815-917.
70. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Heard SE; American Association of Poison Control Centers. 2007 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report. *Clin Toxicol (Phila)* 2008; 46: 927-1057.
71. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. *Clin Toxicol (Phila)* 2009; 47: 911-1084.
72. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL. 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report. *Clin Toxicol (Phila)* 2010; 48: 979-1178.
73. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Dart RC. 2010 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. *Clin Toxicol (Phila)* 2011; 49: 910-41.
74. Anderson D, Reed S, Lintemoot J, et al. A first look at duloxetine (Cymbalta) in a postmortem laboratory. *J Anal Toxicol* 2006; 30: 576-80.
75. Mari F, Gualco B, Rensi R, Bertol E. Acute massive pulmonary thromboembolism due to acute intoxication by duloxetine: a case report. *Cardiovasc Toxicol* 2012; 12: 258-62.