Treatment of Depression in the Elderly: A Review of the Recent Literature on the Efficacy of Single- Versus Dual-Action Antidepressants

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ABSTRACT

Background: Despite the prevalence of depression in the elderly, there is a shortage of randomized controlled studies comparing the efficacy of various antidepressant classes in this population.

Objectives: This review of recent data on the treatment of depression in the elderly examined the relative efficacy of the selective serotonin reuptake inhibitors (SSRIs) and 2 antidepressant classes having broader neuroreceptor activity—the tricyclic antidepressants (TCAs) and the serotonin–norepinephrine reuptake inhibitors (SNRIs). Tolerability was examined as a secondary objective.

Methods: A systematic review of MEDLINE, PsycINFO, and PubMed (January 2003–January 2009) was performed using the terms *antidepressant*, *SSRI*, *SNRI*, *TCA*, *depression*, *randomized controlled trials*, *human trials*, and individual antidepressant names. The criteria for inclusion in the review were a double-blind design, a placebo control or active comparator group, a population exclusively aged ≥59 years, and enrollment of patients with a diagnosis of major depressive disorder.

Results: The literature search identified 18 trials of the treatment of depression in the elderly: 10 compared SSRIs either head to head or versus placebo, 2 compared TCAs with SSRIs, and 6 examined SNRIs (2 vs placebo, 1 vs a TCA, and 3 vs SSRIs). In 2 head-to-head trials, one of which measured efficacy in terms of change in Hamilton Depression Rating Scale (HAM-D) scores and response rates, and the other in terms of a preset 90% CI, TCAs and SSRIs had comparable efficacy. The data from 5 studies using various measures (including changes in Montgomery-Asberg Depression Rating Scale, HAM-D, or Geriatric Depression Scale [GDS] scores; response rates; and remission rates) suggested no additional efficacy benefit for the SNRI venlafaxine compared with SSRIs or TCAs. In a single trial, duloxetine was significantly more effective than placebo in terms of reductions in HAM-D and GDS scores (both, $P < 0.001$).

Conclusion: The available data, although limited, suggest that the dual-action agents (TCAs and SNRIs) do not appear to confer any additional benefits in efficacy over single-action agents (SSRIs) in the treatment of depression in the elderly. (*Clin Ther.* 2009;31: 945–961) © 2009 Excerpta Medica Inc.

Key words: aged, depression, antidepressant therapy, review, efficacy.

INTRODUCTION

Major depressive disorder (MDD) is common in the elderly, with an estimated prevalence of ~3% in the general population[1] and 15% to 25% among nursing home residents.[2] Approximately 15% of the community-dwelling elderly have clinically significant depressive symptoms, and such symptoms are present in ~25% of elderly patients with a chronic medical illness.[3] Despite the high prevalence of depressive illness in this population, it is estimated that clinically significant depression goes untreated in 60% of cases.[4]

Selective serotonin reuptake inhibitors (SSRIs) have superseded tricyclic antidepressants (TCAs) as the most frequently used medications for depression.[5] More recently, the serotonin–norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine have come to play a role in the treatment of late-life depression. In a specific guideline for geriatric depression, a 2001 expert consensus panel recommended venlafaxine as an alternative to SSRIs as a first-line treatment for depression in the elderly and as a preferred agent in those who do not respond to SSRIs.[6] Feighner[7] re-

Accepted for publication March 20, 2009.
doi:10.1016/j.clinthera.2009.05.016
0149-2918/$ - see front matter

ported that venlafaxine appears to have low protein binding, and Ereshefsky and Dugan[8] reported that it has a low potential for pharmacokinetic drug interactions via the cytochrome P450 enzyme system. A review of the cardiovascular profile of duloxetine reported a low occurrence of cardiovascular adverse events (AEs), suggesting that this agent may be an appropriate choice for the treatment of MDD in the elderly.[9] There are also data suggesting that SNRIs may have greater efficacy than SSRIs in the treatment of depression in the general adult population and may have a favorable effect on the pain associated with depression.[10,11]

The results of studies in younger adult populations cannot be generalized to the elderly population, who have altered drug pharmacokinetics as well as chronic medical illnesses that may affect their renal, hepatic, and cardiac function. Drug absorption is variable, volume of distribution is decreased, and mean drug levels are higher in the elderly, all of which may adversely affect their ability to metabolize or excrete some medications.[12] Elderly patients with depression are less likely than younger patients to have a family history of mood disorders and more likely to have evidence of cerebrovascular disease on neuroimaging.[13] Together, these factors contribute to reduced safety and tolerability of antidepressants in the elderly.

Taylor and Doraiswamy[14] conducted a systematic review of all randomized, placebo-controlled trials of antidepressants in patients aged >55 years published through 2003. Twelve trials examined TCAs, 5 examined SSRIs, 2 examined bupropion, and 1 examined mirtazapine; there were no published trials of venlafaxine or nefazodone at the time. In all, 71.5% of the trials reported significantly greater efficacy with drug treatment compared with placebo ($P < 0.05$). Nelson et al[15] conducted a meta-analysis of 10 trials including 13 comparisons (fluoxetine 3, escitalopram 2, sertraline 1, paroxetine 3, citalopram 1, venlafaxine 1, duloxetine 1, and bupropion 1). They found that in adults aged ≥60 years with MDD, second-generation antidepressants were more effective than placebo in terms of both response ($P < 0.001$) and remission ($P < 0.001$), as defined by scores on depression rating scales, although the magnitude of this effect was small and variable. The number needed to treat (NNT) was 13 for response and 20 for remission, implying that for every 100 patients treated, 8 would have a response and 5 would have a remission beyond the effects seen with placebo. The authors cautioned, however, that the benefits of drug treatment needed to be weighed against the rates of AEs requiring discontinuation: they found that for every 2 patients who responded to drug treatment, 1 discontinued prematurely because of AEs.

The question then arises whether the TCAs and SNRIs, which have broader neuroreceptor activity, may be more efficacious than the SSRIs for the treatment of depression in the elderly. Taylor and Doraiswamy[14] found no difference between active agents in studies that included active comparators, but many of these trials were underpowered to detect a significant difference. In addition, given the available trials, they were able to compare only TCAs and SSRIs. TCAs were associated with a numerically lower NNT than SSRIs (5 vs 8, respectively), although the difference between antidepressant classes was not statistically significant. A meta-analysis by Mottram et al[16] reported that SSRIs had equal efficacy to TCAs in the treatment of depression in the elderly and significantly fewer withdrawals due to AEs ($P = 0.007$).

No more recent systematic reviews have specifically compared the efficacy and tolerability of single-action antidepressants (SSRIs) with those of dual-action antidepressants (TCAs and SNRIs) in the treatment of depression in the elderly. Thus, the present systematic review focused on randomized, double-blind trials of pharmacotherapy for depression in the elderly published since 2003. Its primary objective was to compare the efficacy of SSRIs with those of TCAs and SNRIs, with tolerability as a secondary objective.

METHODS

A systematic review of MEDLINE, PsycINFO, and PubMed (January 2003–January 2009) was performed using the terms *antidepressant*, *SSRI*, *SNRI*, *TCA*, *depression*, *randomized controlled trials*, *human trials*, and individual antidepressant names. The criteria for inclusion in the review were a double-blind design, a placebo control or active comparator group, a population exclusively aged ≥59 years, and enrollment of patients with a diagnosis of MDD. The age cutoff of ≥59 years was used to maximize the number of studies included.

Because the objective was to include as broad a patient population as possible given the age restriction, published meeting abstracts that met the inclusion criteria were also considered, as were publications in any language. Studies conducted in the community, nursing

home, outpatient, and hospital settings were eligible for inclusion, as were studies that enrolled patients with comorbid dementia or medical illnesses, and studies of maintenance therapy for depression. Pharmaceutical companies were not contacted.

Abstracts of the publications identified by the literature search were reviewed twice for eligibility by one investigator, and the selections were reviewed by the second investigator. Data were then extracted from the full study reports by one investigator and reviewed by the other.

RESULTS

Of 407 abstracts initially reviewed, 389 studies were excluded and 18 met the criteria for inclusion in the review.[17–34] All were randomized, double-blind studies with either a placebo or active control group. With the exception of 2 studies that did not specify approval or method of consent,[19,26] all study reports mentioned obtaining informed consent from participants or their caregivers, and receiving approval from an institutional review board or equivalent ethics committee.

The trials had considerable heterogeneity in their study samples, designs, dosing strategies, and durations of treatment (**Table I**). There were also differences in their inclusion criteria with respect to the diagnosis of MDD or medical and psychiatric comorbidities. The studies used various rating scales as primary outcome measures, but the most commonly used were the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS). Other instruments used were the Geriatric Depression Scale (GDS) and the Clinical Global Impression (CGI) scale.

The definitions of response and remission also differed across studies. Generally, *response* was defined as a score of 1 or 2 on the CGI-Improvement (CGI-I) subscale or as a 50% reduction in total scores on the MADRS and/or HAM-D. *Remission* was variously defined as MADRS scores ranging from <9 to <12 or HAM-D scores ranging from <7 to <10. The change in MADRS scores in the various studies is summarized in **Table II**, and the change in HAM-D scores is summarized in **Table III**. The results for secondary outcome measures are presented in **Table IV**.

Selective Serotonin Reuptake Inhibitors

Because of their favorable tolerability profiles, SSRIs have been increasingly used in the treatment of geriatric depression. They are now more frequently used for this indication than the TCAs.[5]

Escitalopram and Citalopram

Bose et al[17] conducted a 12-week, randomized, double-blind, placebo-controlled study of escitalopram in outpatients aged >60 years who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for MDD and were experiencing an ongoing major depressive episode of at least 4 weeks' duration. Eligible patients were required to have a Mini–Mental State Examination (MMSE) score >24 and a MADRS score >22 at baseline. Escitalopram was dosed flexibly over the range from 10 to 20 mg/d (mean, 14 mg/d). The study enrolled 264 patients (60% female; predominantly white; ~22% aged >75 years). At the end of the study, there were no significant differences between escitalopram and placebo in terms of the change from baseline in total MADRS score; rates of response, defined as a >50% reduction in MADRS score (46% and 38%, respectively); or rates of remission, defined as a MADRS score <10 (34% and 29%). Discontinuation rates were 26.2% and 18.7% in the respective groups.

Gorwood et al[18] conducted a maintenance trial in which patients who had experienced remission during a 12-week study of open-label escitalopram, flexibly dosed from 10 to 20 mg, were randomized to receive either double-blind escitalopram 10 or 20 mg or placebo on an outpatient basis for an additional 24 weeks. Eligible participants were aged ≥65 years, met *DSM-IV* criteria for moderate to severe MDD, and had a MADRS score ≥22 and MMSE score ≥24. The maintenance study included 305 patients (79% female; mean [SD] age, 73 [5.4] years; >33% aged >75 years). At the end of the continuation phase, escitalopram was associated with a significant decrease in rates of recurrence, defined as a MADRS score ≥22, compared with placebo (9% vs 33%; $P < 0.001$). In a secondary analysis of time to relapse based on a Cox proportional hazards model, the risk of relapse was 4.44 times higher in the placebo group compared with the escitalopram group (χ^2 test, 22.9, $df = 1$; $P < 0.001$). Dropout rates were 15% in the escitalopram group and 41% in the placebo group.

Kasper et al[19] conducted an 8-week, randomized, double-blind comparison of escitalopram, fluoxetine, and placebo in outpatients aged ≥65 years who met *DSM-IV* criteria for MDD, had a MADRS score of

Table I. Designs of the studies included in the review.

Antidepressant Class	Authors	Population	Regimens	No. of Patients	Duration
SSRIs	Bose et al[17]	Outpatients	Escitalopram 10–20 mg/d (titrated) Placebo	130 134	12 wk
	Gorwood et al[18]	Outpatients who had remission with 12 wk of open-label escitalopram	Escitalopram 10 or 20 mg/d Placebo	152 153	36 wk
	Kasper et al[19]	Outpatients	Escitalopram 10 mg/d (fixed dose) Fluoxetine 20 mg/d (fixed dose) Placebo	173 164 181	8 wk
	Roose et al[20]	Outpatients	Citalopram 10–40 mg/d (titrated) Placebo	84 90	8 wk
	Rapaport et al[21]	Outpatients	Paroxetine IR 10–40 mg/d (titrated) Paroxetine CR 12.5–50 mg/d (titrated) Placebo	106 104 109	12 wk
	Dombrovski et al[22]	Outpatients who responded to open-label paroxetine + ITP	Paroxetine 10–40 mg/d (titrated) + ITP Paroxetine 10–40 mg/d (titrated) + CM Placebo + ITP Placebo + CM	28 35 35 18	1 y
	Rossini et al[23]	Inpatients, including those with bipolar depression	Sertraline 150 mg/d (fixed dose) Fluvoxamine 200 mg/d (fixed dose)	48 40	7 wk
	Schneider et al[24]	Outpatients who responded to open-label sertraline and had remission during 16- to 20-wk continuation phase	Sertraline 50–100 mg/d (titrated) Placebo	371 376	8 wk
	Wilson et al[25]	Outpatients	Sertraline 50–150 mg/d (titrated) Placebo	56 57	Up to 100 wk
	Sheikh et al[26]	Outpatients with/without medical comorbidities	Sertraline 50–100 mg/d (titrated) Placebo	360 368	8 wk

(continued)

Table I (continued).

Antidepressant Class	Authors	Population	Regimens	No. of Patients	Duration
TCAs	Rosenberg et al[27]	Outpatients	Amitriptyline 50–100 mg/d (titrated) Citalopram 20–40 mg/d (titrated)	136 155	12 wk
	Wehmeier et al[28]	Inpatients (85.4%) and outpatients	Trimipramine 150 mg/d (fixed dose) Fluoxetine 20 mg/d (fixed dose)	21 20	6 wk
SNRIs	Allard et al[29]	Outpatients	Venlafaxine ER 75–150 mg/d (titrated) Citalopram 20–30 mg/d (titrated)	76 75	6 mo
	de Vasconcelos Cunha et al[30]	Outpatients with mild to moderate dementia	Venlafaxine IR 37.5–131.25 mg/d (titrated) Placebo	14 17	6 wk
	Oslin et al[31]	Nursing home residents	Venlafaxine IR 18.75–150 mg/d (titrated) Sertraline 25–10 mg/d	27 25	10 wk
	Schatzberg and Roose[32]	Outpatients	Venlafaxine IR 37.5–225 mg/d (titrated) Fluoxetine 20–60 mg/d (titrated) Placebo	104 100 96	8 wk
	Gastó et al[33]	Inpatients and outpatients	Venlafaxine ER 225–300 mg/d (titrated) Nortriptyline 50–100 mg/d (titrated)	34 34	6 mo
	Raskin et al[34]	Outpatients	Duloxetine 60 mg/d (fixed dose) Placebo	207 104	8 wk

SSRIs = selective serotonin reuptake inhibitors; IR = immediate release; CR = controlled release; ITP = interpersonal therapy (45 minutes monthly); CM = clinical management (30-minute appointment monthly, targeting symptoms and adverse effects); TCAs = tricyclic antidepressants; SNRIs = serotonin–norepinephrine reuptake inhibitors; ER = extended release.

Table II. Change in Montgomery-Asberg Depression Rating Scale (MADRS) scores in studies in which this was a primary efficacy end point.*

Antidepressant Class	Authors	Comparators	MADRS Score		
			Baseline	Final	Mean Change (or Related Outcome)
SSRIs	Bose et al[17]	Escitalopram Placebo	29.4 28.4	NR	0.86 (P = 0.29 vs placebo) 6.62
	Gorwood et al[18]	Escitalopram Placebo	5.1 5.1	NR	Time to relapse and relapse prevention: both, P < 0.001 vs placebo; NNT for relapse prevention = 5
	Kasper et al[19]	Escitalopram Fluoxetine Placebo	28.2 28.5 28.6	NR	P = NS, escitalopram vs placebo; P < 0.01, fluoxetine vs placebo
SNRIs	Allard et al[29]	Venlafaxine Citalopram	27.6 27.0	9.6 9.6	P = NS at wk 8 and 22
	de Vasconcelos Cunha et al[30]	Venlafaxine Placebo	24.5 24.5	11.4 12.2	P = 0.552

SSRIs = selective serotonin reuptake inhibitors; NR = not reported; NNT = number needed to treat; SNRIs = serotonin–norepinephrine reuptake inhibitors.
*Lower scores indicate less depression.

22 to 40, and had an MMSE score ≥22. Escitalopram and fluoxetine were given at fixed doses of 10 and 20 mg/d, respectively. A total of 518 patients were randomized to treatment (3:1 female:male ratio; mean age, 75 years; 99%–100% white; mean MADRS score, 28.6). There was no difference in the change in MADRS scores between escitalopram and placebo; there was, however, a significant difference between fluoxetine and placebo (P < 0.01). There were no significant differences between groups in terms of rates of remission, defined as a >50% reduction in MADRS score (40% escitalopram, 30% fluoxetine, 42% placebo), or rates of response, defined as a MADRS score <12 (46%, 37%, and 47%, respectively). The fluoxetine group had a significantly higher dropout rate compared with escitalopram and placebo (26%, 17%, and 11%; P < 0.05 and P < 0.001, respectively).

Roose et al[20] compared citalopram and placebo in an 8-week, randomized, placebo-controlled trial in patients aged ≥75 years who were not living in a residential setting, had nonpsychotic unipolar depression with a current episode of at least 4 weeks' duration, and had a baseline HAM-D 21 score ≥20. Citalopram was flexibly dosed over the range from 10 to 40 mg. The study enrolled 174 patients (58% female; mean age, 79.6 years; mean HAM-D 21 score, 24.3). There were no significant differences between escitalopram and placebo in terms of change in HAM-D 21 scores; rates of remission, defined as a HAM-D 21 score <10 (34% and 29%, respectively); or rates of response, defined as a >50% reduction in HAM-D 21 score (46% and 38%). Dropout rates were 21% in the citalopram group and 12% in the placebo group.

The results of these studies suggest that the duration of treatment may contribute to efficacy. The 36-week maintenance study indicated a benefit to continued treatment with escitalopram,[18] whereas the relatively short durations of the studies of acute treatment with escitalopram and citalopram may have contributed to the lack of significant findings.

Table III. Change in Hamilton Depression Rating Scale (HAM-D) scores in studies in which this was a primary efficacy end point.*

Antidepressant Class	Authors	Comparators	HAM-D 17 Score: Baseline	HAM-D 17 Score: Final	HAM-D 17 Score: Mean Change (or Related Outcome)
SSRIs	Rapaport et al[21]	Paroxetine IR	22.3	10.0	–12.3 ($P < 0.001$ vs placebo)
		Paroxetine CR	22.1	10.0	–12.1 ($P < 0.001$ vs placebo)
		Placebo	22.1	12.6	–9.5
	Dombrovski et al[22]	Paroxetine + ITP	6.0	NR	NR
		Paroxetine + CM	4.9		
		Placebo + ITP	5.5		
		Placebo + CM	5.8		
	Schneider et al[24]	Sertraline	21.4	14.0	–7.4 ($P = 0.01$ vs placebo)
		Placebo	21.4	14.8	–6.6
	Wilson et al[25]	Sertraline	20.7	NR	$P = 0.21$
		Placebo	20.3		
	Sheikh et al[26]	Sertraline	21.4	NR	–7.88 ($P = 0.02$ vs placebo)
		Placebo	21.4		–6.37
TCAs	Rosenberg et al[27]	Amitriptyline Citalopram	NR	NR	P = NS
	Wehmeier et al[28]	Trimipramine	27.9	12.1	P = NS
		Fluoxetine	28.1	16.2	
SNRIs	Oslin et al[31]	Venlafaxine IR	20.3	15.7	P = NS
		Sertraline	20.2	12.2	
		Nortriptyline	25.85		
	Gastó et al[33]	Venlafaxine ER	27.18	NR	P = NS
	Raskin et al[34]	Duloxetine	22.4	NR	–6.49 ($P < 0.011$ vs placebo)
		Placebo	22.0		–3.72

Antidepressant Class	Authors	Comparators	HAM-D 21 Score: Baseline	HAM-D 21 Score: Final	HAM-D 21 Score: Mean Change (or Related Outcome)
SSRIs	Roose et al[20]	Citalopram	24.4	NR	P = NS
		Placebo	24.2		
	Rossini et al[23]	Sertraline	29.23	11.27	Baseline score: $P = 0.03$ between groups; final score: P = NS; speed of response: $P < 0.001$, fluvoxamine vs sertraline
		Fluvoxamine	31.23	7.56	
SNRIs	Schatzberg and Roose[32]	Venlafaxine IR	24	NR	P = NS, both active treatments vs placebo and vs each other
		Fluoxetine	27		
		Placebo	27		

SSRIs = selective serotonin reuptake inhibitors; IR = immediate release; CR = controlled release; ITP = interpersonal therapy (45 minutes monthly); NR = not reported; CM = clinical management (30-minute appointment monthly, targeting symptoms and adverse effects); TCAs = tricyclic antidepressants; SNRIs = serotonin–norepinephrine reuptake inhibitors; ER = extended release.
*Lower scores indicate greater improvement.

Table IV. Results for secondary outcomes.*

Antidepressant Class	Authors	Comparators	Secondary Outcomes
SSRIs	Bose et al[17]	Escitalopram Placebo	≥50% Reduction in MADRS score: 46% and 38%, respectively; MADRS score <10: 34% and 29%; CGI-I score: 2.6 and 2.7 (all, *P* = NS)
	Gorwood et al[18]	Escitalopram Placebo	Change in GDS score: 0.05 vs 3.87, respectively (*P* < 0.001); CGI score 1 or 2: 90.8% vs 2.1% (*P* < 0.001); ≥50% reduction in MADRS score: 90.8% vs 66.7% (*P* < 0.001)
	Kasper et al[19]	Escitalopram Fluoxetine Placebo	≥50% Reduction in MADRS score: 46%, 37%, and 47%, respectively; MADRS score <12: 40%, 30%, and 42% (*P* < 0.05, escitalopram vs fluoxetine); CGI-S score: 2.64, 3.02, and 2.70 (*P* < 0.05, escitalopram vs fluoxetine)
	Roose et al[20]	Citalopram Placebo	≥50% Reduction in HAM-D score: 40.5% and 37.8%, respectively (*P* = 0.32); HAM-D score <10: 34.5% and 33.3% (*P* = 0.59); CGI score 1 or 2: 44.1% and 43.3% (*P* = 0.22)
	Rapaport et al[21]	Paroxetine IR Paroxetine CR Placebo	CGI score 1 or 2: 65% (*P* = 0.06 vs placebo), 72% (*P* < 0.002 vs placebo), and 52%, respectively; HAM-D score <7: 44% (*P* = 0.01 vs placebo), 43% (*P* = 0.009 vs placebo), and 26%
	Rossini et al[23]	Sertraline Fluvoxamine	HAM-D score <8: 55.6% and 71.8%, respectively (*P* = 0.12)
	Schneider et al[24]	Sertraline Placebo	CGI score <2: 45% vs 35%, respectively (*P* = 0.005); time to response: 57 vs 61 d (*P* = 0.002); ≥50% reduction in HAM-D score: 35% vs 26% (*P* = 0.007)
	Sheikh et al[26]	Sertraline Placebo	CGI-I score 1 or 2: *P* = 0.001
TCAs	Wehmeier et al[28]	Trimipramine Fluoxetine	≥50% Reduction in HAM-D score or HAM-D score <10: 60.0% and 57.1%, respectively; ≥50% reduction in MADRS score: 70.0% and 57.1%; CGI score >1: 81% and 70% (all, *P* = NS)
SNRIs	Allard et al[29]	Venlafaxine ER Citalopram	CGI score 1 or 2: 87.7% and 86.4%, respectively; GDS-20 score: 4.4 and 4.9
	de Vasconcelos Cunha et al[30]	Venlafaxine IR Placebo	≥50% Reduction in MADRS score: 57.1% and 64.7%, respectively (*P* = 0.667); CGI score: *P* = 0.19
	Oslin et al[31]	Venlafaxine IR Sertraline	CGI score: 3.0 and 2.3, respectively (*P* = 0.098); change in GDS score: −0.8 and −3.5 (*P* = 0.151); change in CSDD score: −4.0 and −8.5 (*P* = 0.008)

(continued)

Table IV (continued).

Antidepressant Class	Authors	Comparators	Secondary Outcomes
SNRIs (continued)	Schatzberg and Roose[32]	Venlafaxine IR Fluoxetine Placebo	≥50% Reduction in HAM-D or MADRS score: $P = 0.7220$ and $P = 0.732$, respectively, vs placebo; HAM-D score <7: 27%, 20%, and 24%, respectively (P = NS)
	Raskin et al[34]	Duloxetine Placebo	Change in GDS score: –4.07 and –1.34, respectively ($P < 0.001$); composite cognitive score: 1.95 and 0.76 ($P = 0.013$); VAS for back pain ($P < 0.01$); VAS for time in pain while awake ($P < 0.05$)

SSRIs = selective serotonin reuptake inhibitors; MADRS = Montgomery-Asberg Depression Rating Scale; CGI-I = Clinical Global Impression–Improvement; GDS = Geriatric Depression Scale; CGI-S = CGI-Severity of Illness; HAM-D = Hamilton Depression Rating Scale; IR = immediate release; CR = controlled release; TCAs = tricyclic antidepressants; SNRIs = serotonin–norepinephrine reuptake inhibitors; ER = extended release; CSDD = Cornell Scale for Depression in Dementia; VAS = visual analog scale.

*In these studies, *response* was generally defined as a score of 1 or 2 on the CGI-I subscale or as a 50% reduction in total scores on the MADRS and/or HAM-D. *Remission* was variously defined as a MADRS score ranging from <9 to <12 or a HAM-D score ranging from <7 to <10. On all instruments, lower scores indicated greater reduction or improvement in depressive symptoms.

Paroxetine

Rapaport et al[21] conducted a 12-week, randomized, double-blind, flexible-dose study of paroxetine immediate release (IR), paroxetine controlled release (CR), and placebo in outpatients aged ≥60 years with a diagnosis of MDD (*DSM-IV* criteria) and a HAM-D 17 score ≥18. Doses of paroxetine IR ranged from 10 to 40 mg/d (mean, 25.7 mg/d), and doses of paroxetine CR ranged from 12.5 to 50 mg/d (mean, 30.4 mg/d). The study enrolled 319 patients (mean age, ~70 years; 95.3% white), >90% with a chronic (>2 years) depressive disorder and a medical diagnosis (other than depression) requiring medication. Both paroxetine IR and paroxetine CR were associated with significant improvements compared with placebo in HAM-D scores (–12.3, –12.1, and –9.5, respectively; both, $P < 0.001$); remission rates, defined as a HAM-D 17 score <7 (44% [$P = 0.01$], 43% [$P = 0.009$], and 26%); and response rates, defined as a CGI-I score of 1 or 2 (65% [$P = 0.06$], 72% [$P < 0.002$], and 52%). Dropout rates were 28% for paroxetine IR, 22% for paroxetine CR, and 23% for placebo.

Dombrovski et al[22] conducted a 1-year, randomized, 2-by-2 maintenance study comparing paroxetine with placebo and monthly interpersonal psychotherapy (ITP) with clinical management in patients aged ≥70 years with current MDD (*DSM-IV* criteria) without psychosis, a HAM-D 17 score ≥15, and a MMSE score ≥17. One hundred ninety-five patients entered an 8-week, open-label trial of the combination of paroxetine and weekly ITP; of these, 151 patients subsequently entered a 16-week, open-label continuation phase in which they received paroxetine and alternate-week ITP. One hundred sixteen patients (65% female; 88% white) who did not relapse during the continuation phase were randomized to 1 of the following double-blind maintenance groups: paroxetine with monthly ITP, paroxetine with clinical management, placebo with monthly ITP, and placebo with clinical management. There were significant differences between the groups receiving paroxetine and the groups receiving placebo in terms of changes in mean scores on the 36-item Short Form Health Survey (SF-36) measure of social function ($P = 0.02$), SF-36 measure of emotional role function ($P = 0.007$), and health-related quality of life (HRQOL) ($P = 0.04$). There were no significant differences in overall HRQOL, any SF-36 domain, or recurrence rates (defined as a HAM-D 17 score >15, with results of the Structured Clinical Interview for depression) between ITP and clinical management. Recurrence rates in the groups that received paroxetine with ITP, paroxetine with clinical management, placebo with ITP, and placebo with clinical management were 43%, 40%, 40%, and 39%, respectively. Dropout rates were 39%, 46%, 66%, and 67%. The results suggested that paroxetine was efficacious in the treatment of acute depression in the elderly and was associated with maintenance of overall functioning over the long term.

Sertraline

Rossini et al[23] conducted a 7-week, randomized, double-blind, parallel-group comparison of sertraline 150 mg/d and fluvoxamine 200 mg/d in patients aged ≥59 years who were hospitalized for a major depressive episode without psychotic features associated with a diagnosis of MDD or bipolar disorder, were receiving maintenance treatment with mood stabilizers, and had an MMSE score ≥23 and a HAM-D 21 score ≥21. The study enrolled 88 patients (69.3% female; mean age, ~68 years; 79.5% with unipolar depression). There were no significant differences between the sertraline and fluvoxamine groups in terms of the change in HAM-D 21 score (–17.96 and –23.67, respectively) or rates of remission, defined as a HAM-D 21 score <8 (55.6% and 71.8%). Fluvoxamine was associated with significantly greater speed of response compared with sertraline ($P < 0.001$); given the nonsignificant differences in HAM-D 21 scores and remission rates, it is not known whether the significant difference in speed of response is clinically significant. Dropout rates were 6.3% for sertraline and 2.5% for fluvoxamine.

Schneider et al[24] conducted an 8-week, randomized, double-blind, placebo-controlled study of sertraline in community-dwelling patients aged ≥60 years with a diagnosis of MDD without psychotic features (*DSM-IV* criteria) of at least 4 weeks' duration and a HAM-D 17 total score ≥18. Sertraline was flexibly dosed from 50 to 100 mg/d; by the final week of the study, 63% of patients were receiving sertraline 100 mg/d. The intent-to-treat analysis included 747 subjects (54.6% female; 93% white; mean age, 69.8 years). The sertraline group had significant reductions compared with placebo in terms of the mean reduction in HAM-D 17 score (–7.4 vs –6.6, respectively; $P = 0.01$) and rates of response, defined as a >50% reduction in HAM-D 17 score (35% vs 26%; $P = 0.007$). A signifi-

cant treatment effect was seen by week 2 (P = 0.01). Dropout rates were 21% in the sertraline group and 15% in the placebo group.

Wilson et al[25] reported the results of a randomized, double-blind, placebo-controlled trial of sertraline maintenance therapy in outpatients aged ≥65 years who had a diagnosis of MDD (*DSM, Third Edition Revised* [*DSM-III-R*]), a Geriatric Mental State–AGECAT (Automated *Geriatric* Examination for Computer Assisted Taxonomy) depression level ≥3, a HAM-D 17 score ≥18, and an MMSE score >11. This maintenance trial included patients who had first responded to 8 weeks of open-label sertraline and had then experienced a remission during a 16- to 20-week continuation phase. Patients meeting the criteria for the maintenance phase were randomized to receive sertraline 50 to 150 mg/d (at the response dose) or placebo, for 100 weeks. The maintenance study included 113 patients (70.8% female; mean age, 76.7 years; mean HAM-D 17 score, 20.5). There were no significant differences between sertraline and placebo in prevention of recurrence, defined as a HAM-D 17 score >13 (–7.9%; 95% CI, –28.1 to 12.2); there was an 8.4% reduction in the risk of recurrence over 100 weeks with sertraline compared with placebo. More than half of recurrences occurred in the first 26 weeks of the maintenance phase (57% and 60%, respectively). Over the entire study period, 38.6% of patients in the sertraline group and 31.1% of patients in the placebo group had no recurrence of depression. Dropout rates were 73% in the sertraline group and 79% in the placebo group.

Sheikh et al[26] conducted an 8-week, randomized, double-blind, placebo-controlled study of sertraline, flexibly dosed from 50 to 100 mg/d in patients aged ≥60 years (at least 75% aged >65 years) with MDD (*DSM-IV* criteria), a depressive episode of at least 4 weeks' duration, and a HAM-D 17 score ≥18, with a score ≥2 on item 1 (depressed mood). The intent-to-treat analysis included 728 patients, stratified based on the lack or presence of medical comorbidities (vascular disease, diabetes mellitus, and arthritis). The mean age of the 127 patients without the 3 main forms of medical comorbidity was 68.1 years, compared with 70.9 years in the 442 patients with the 3 main forms of medical comorbidity (P < 0.05). Patients without medical comorbidities were 41% female, whereas those with medical comorbidities were 59% male (P < 0.05). There were no significant differences in baseline HAM-D 17 scores between those without and with comorbidities (mean, 21.1 and 21.4, respectively). When all patients were included, the sertraline group had a significant improvement in HAM-D 17 scores compared with placebo (–7.88 vs –6.37, respectively; P = 0.02). There was no significant treatment-by-comorbidity interaction, although those with medical comorbidities had a significantly earlier time to response with sertraline compared with placebo (P = 0.006). Dropout rates were 27.1% in those with no comorbidity receiving sertraline, 22.1% in those with no comorbidity receiving placebo, 18.1% in those with comorbidity receiving sertraline, and 16.3% in those with comorbidity receiving placebo.

Tricyclic Antidepressants

Most studies of the efficacy of TCAs were conducted in the 1980s, before the advent of the SSRIs. The literature search identified 2 recent head-to-head efficacy comparisons of TCAs and SSRIs in the treatment of depression in the elderly.

Rosenberg et al[27] conducted a 12-week, randomized, double-blind, parallel-group study comparing the efficacy of amitriptyline and citalopram in the treatment of outpatients aged ≥65 years with a diagnosis of MDD or dysthymia (*DSM-III-R* criteria), an MMSE score ≥20, and a HAM-D 17 score ≥13. Dosing was flexible, ranging from 50 to 100 mg/d for amitriptyline and from 20 to 40 mg/d for citalopram. Two hundred twenty-one patients were female and 70 were male; the mean age of the study sample was 75.5 years, and only 2% of patients in each arm had a diagnosis of dysthymia alone. Within the preset 90% CI of –0.25 to 1.92 for change in the mean total HAM-D 17 score, there was no significant difference in efficacy between the 2 study medications. Rates of response and remission were not reported. Dropout rates were 29% for amitriptyline and 25% for citalopram.

Wehmeier et al[28] conducted a 6-week, randomized, double-blind, parallel-group comparison of fixed doses of trimipramine 150 mg/d and fluoxetine 20 mg/d in a predominantly inpatient (85.4%) setting. The inclusion criteria were age >60 years, a diagnosis of MDD (*DSM-III-R* criteria), and a HAM-D 17 score ≥16. Thirty-nine of the 41 subjects were female, and the mean age of the study sample was ~72 years. There was no significant difference between trimipramine and fluoxetine in terms of reduction in HAM-D 17 scores (–15.8 and –11.9, respectively) and rates of re-

sponse, defined as a >50% reduction in HAM-D 17 score (60.0% and 57.1%). Three of 21 patients (14.3%) in the trimipramine group and 5 of 20 patients (25.0%) in the fluoxetine group discontinued prematurely.

Serotonin–Norepinephrine Reuptake Inhibitors

The results of previous studies in the general adult population suggested that patients may respond more rapidly or more completely to venlafaxine than to SSRIs.[10,35] However, before the present review, there was limited evidence for the use of SNRIs in the treatment of depression in the elderly.[14] The literature search identified 5 recent randomized studies that compared venlafaxine with SSRIs, TCAs, or placebo, and 1 placebo-controlled study of duloxetine in the treatment of depression in the elderly.

Venlafaxine

Allard et al[29] conducted a 6-month, randomized, double-blind, parallel-group comparison of venlafaxine extended release (ER) and citalopram in outpatients aged ≥65 years with MDD (*DSM-IV* criteria), a MADRS score ≥20, and a minimum MMSE score of 24. The venlafaxine dose was initiated at 37.5 mg during the first week and increased to 75 mg/d during the second week; after 2 weeks at 75 mg/d, the dose could be titrated to 150 mg/d if there had been no response (54.7% of patients). Similarly, the citalopram dose was increased to 20 mg/d by week 2 and then increased to 30 mg/d if there had been no response after another 2 weeks (55.3% of patients). One hundred fifty-one patients (~75% female; mean age, 73 years; mean MADRS score, 27) were randomized to treatment. There were no significant differences in efficacy between the 2 groups. MADRS scores declined rapidly, with no significant difference in the pattern of reduction between groups; scores were 9.6 in both groups at week 22. Rates of response, defined as a >50% reduction in MADRS score, were 75% and 73% in the venlafaxine ER and citalopram groups, respectively, at week 8; up to 93% of patients met the criterion for response by week 22. Rates of remission, defined as a MADRS score <10, did not differ significantly between groups (19% and 23%). Dropout rates were 22% in both groups.

de Vasconcelos Cunha et al[30] conducted a 6-week, randomized, double-blind, placebo-controlled comparison of venlafaxine IR and placebo in outpatients aged ≥60 years who lived at home, had mild to moderate dementia (*DSM-IV* and Cornell Scale for Depression in Dementia criteria), and had an MMSE score between 10 and 24. The dose of venlafaxine IR was titrated flexibly, ranging from 37.5 to 131.25 mg/d (mean, 75 mg/d). The study sample included 31 patients, 74.2% of whom were female, with a mean age of 77.6 years and a mean MADRS score of 24.5. There were no significant differences between venlafaxine IR and placebo in terms of change in MADRS score (–13.1 and –12.3, respectively); rates of response, defined as a >50% reduction in MADRS (57.1% and 64.7%); or CGI scores. Dropout rates were 43% for venlafaxine IR and 18% for placebo; although not statistically significant, the numerical difference may be of clinical significance.

In a double-blind, parallel-group study by Oslin et al,[31] elderly nursing home residents were randomized to receive venlafaxine IR or sertraline for 10 weeks. Inclusion criteria included a diagnosis of MDD, minor depression, dementia with depression, or dysthymic disorder; significant dysphoria (GDS score ≥10 and/or a score >2 on item 1 [depressed mood] of the HAM-D); duration of symptoms >1 month; HAM-D 17 score >12; and Blessed Information-Memory-Concentration Test score <21. Both medications could be titrated based on response and tolerability; it took at least 2 weeks to attain a venlafaxine IR dose of 75 mg/d and a sertraline dose of 50 mg/d. Doses of venlafaxine IR ranged from 18.75 to 150 mg/d, and doses of sertraline ranged from 25 to 100 mg/d. The study included 52 patients (29 men, 23 women; mean age, 82.5 years; 40 white, 12 black; 80.8% with MDD). There was no significant difference in the change in total HAM-D scores between the venlafaxine IR and sertraline groups (–4.6 and –8.0, respectively). Significantly more patients in the venlafaxine IR group discontinued the study compared with the sertraline group (56% vs 20%; $P = 0.002$).

Schatzberg and Roose[32] conducted an 8-week, randomized, double-blind study comparing venlafaxine IR and fluoxetine with placebo in outpatients aged ≥65 years who were not living in a residential setting, had a diagnosis of unipolar depression (*DSM-IV* criteria) with a current episode of at least 4 weeks' duration, and had a HAM-D 21 score ≥20. With flexible titration, venlafaxine IR doses ranged from 37.5 to 225 mg/d and fluoxetine doses ranged from 20 to 60 mg/d. The sample consisted of 300 patients (56% female; mean age, 71 years; 93% white; mean HAM-D 21

score, ~24). There were no significant differences between venlafaxine IR, fluoxetine, and placebo in terms of change in MADRS scores, response rates (≥50% reduction in HAM-D 21 score), or remission rates (HAM-D 21 score <7) (27%, 20%, and 24%, respectively). Rates of discontinuation were 36%, 30%, and 24%, and did not differ significantly between groups.

Gastó et al[33] conducted a 6-month, randomized, single-blind, parallel-group trial comparing venlafaxine ER and nortriptyline in inpatients and outpatients aged ≥65 years who had a diagnosis of unipolar major depression with or without endogenous or psychotic features, with symptoms present for at least 1 month. Venlafaxine ER was initiated at 75 mg/d and increased to 150 and 225 mg/d after 4 and 8 days, respectively; the dose could be increased to 300 mg/d at 2 weeks. Nortriptyline was initiated at 12.5 mg/d and increased to 25 and 50 mg/d after 4 and 8 days, respectively. Plasma nortriptyline concentrations were determined after 1 week of stable dosing, and the dose was adjusted to achieve blood levels between 80 and 120 ng/mL (maximum dose, 100 mg/d). The study population consisted of 68 patients (~66% female; mean age, 71.44 and 70.21 years in the venlafaxine ER and nortriptyline groups, respectively) with moderate to severe symptoms. All nortriptyline recipients achieved target plasma levels during the first month of treatment. Of the 34 patients in the venlafaxine ER group, 22 had a remission, defined as a HAM-D 17 score <7; of the remainder, 7 did not have a remission and 5 dropped out, for a 71% intent-to-treat remission rate. Of the 34 patients in the nortriptyline group, 21 had a remission, 7 did not, and 6 dropped out, for an intent-to-treat remission rate of 70%. There were no significant differences between groups in rates of remission or discontinuation (15% venlafaxine ER, 18% nortriptyline).

Duloxetine

Raskin et al[34] conducted an 8-week, randomized, double-blind, placebo-controlled comparison of a fixed dose of duloxetine 60 mg/d and placebo (2:1 ratio) in outpatients aged ≥65 years with a diagnosis of MDD (*DSM-IV* criteria), a HAM-D 17 score ≥18, an MMSE score ≥20, and 1 previous episode of depression. The study population consisted of 311 patients (59.5% female; mean age, ~73 years; 78% white; mean HAM-D 17 score, 22). There were significant differences between the duloxetine and placebo groups in terms of change in HAM-D scores (–6.49 vs –3.72, respectively; $P < 0.001$); change in GDS score (–4.07 vs –1.34; $P < 0.001$); a protocol-specified composite cognitive score (1.95 vs 0.76; $P = 0.013$); and visual analog scale scores for back pain ($P < 0.01$) and time in pain while awake ($P < 0.05$). Dropout rates did not differ significantly between groups (21.7% and 23.1%).

TOLERABILITY

Although the primary purpose of this literature review was to compare the efficacy of various antidepressant classes, tolerability is an important component of the treatment of geriatric depression. Therefore, the following sections summarize tolerability data from the studies included in the efficacy review.

Selective Serotonin Reuptake Inhibitors

The most common treatment-emergent AEs with escitalopram in the study by Bose et al[17] were headache (19.2%), nausea (15.4%), diarrhea (14.6%), and dry mouth (10.8%). Only 1 subject each in the escitalopram and placebo groups discontinued prematurely because of a serious AE. In the study by Gorwood et al,[18] 1.3% of escitalopram recipients and 3.9% of placebo recipients withdrew due to AEs. AEs occurred in 40.1% of the escitalopram group and 41.2% of the placebo group; the majority were of mild to moderate severity. Dizziness (4.6%) was the most commonly reported AE. In the study by Kasper et al,[19] rates of withdrawal due to AEs were 9.8% in the escitalopram group, 12.2% in the fluoxetine group, and 2.8% in the placebo group. Overall, AEs occurred in 50.5%, 56.7%, and 53.3% of the respective groups. The most commonly reported AEs were nausea in the escitalopram and fluoxetine groups (6.9% and 7.3%, respectively), and headache in the placebo group (8.3%). In the study by Roose et al,[20] discontinuations due to AEs occurred in 10.7% of the citalopram group and 1.1% of the placebo group ($P = 0.008$). The most commonly reported AEs in the citalopram group were dry mouth (14.9%), headache (11.5%), constipation (11.5%), and dyspepsia (10.3%).

In the study of paroxetine by Rapaport et al,[21] rates of withdrawal due to AEs were 12.5% in the group that received paroxetine CR, 16.0% in the group that received paroxetine IR, and 8.3% in the placebo group. AEs reported by >10% of those receiving paroxetine IR or CR were somnolence, dry mouth, headache, abnormal ejaculation, diarrhea,

asthenia, nausea, constipation, dyspepsia, and decreased appetite. Of the 63 patients in the paroxetine groups in the study by Dombrovski et al,[22] 1 discontinued because of sexual dysfunction, 1 due to psychosis, 1 because of medical problems, and 2 due to nonadherence.

In the comparison of sertraline and fluvoxamine by Rossini et al,[23] there were 3 discontinuations due to AEs in the sertraline group and 1 in the fluvoxamine group. The most common AEs were gastric symptoms (19%), headache (9%), agitation (9%), and somnolence (7%). In the study by Schneider et al,[24] 14% of the sertraline group and 5% of the placebo group withdrew from the study due to AEs. AEs reported by >10% of the sertraline group were diarrhea (19%), headache (17%), nausea (16%), and somnolence (10%). Two patients in each group dropped out of the study by Wilson et al,[25] although specific AEs were not reported. In the study by Sheikh et al,[26] the presence of medical comorbidities was not associated with increased rates of discontinuation due to AEs, which were 11.9% in those with no comorbidities receiving sertraline, 2.9% in those with no comorbidities receiving placebo, 11.3% in those with comorbidities receiving sertraline, and 5.4% in those with comorbidities receiving placebo. AEs reported by >10% of the sertraline group were nausea, dizziness, headache, diarrhea, dry mouth, insomnia, and drowsiness.

Tricyclic Antidepressants

In the study by Rosenberg et al,[27] significantly more patients reported no AEs in the citalopram group compared with the amitriptyline group (50% vs 31%, respectively; $P = 0.001$). AEs occurring in ≥10% of patients in the amitriptyline group were dry mouth (45.0%) and constipation (12.2%); AEs occurring in ≥10% of patients in the citalopram group were nausea (12.6%) and dry mouth (12.6%).

In the study by Wehmeier et al,[28] AEs were reported in 66.7% of the trimipramine group and 54.5% of the fluoxetine group. The most common AEs in the trimipramine group were gastrointestinal complaints (14%), cardiac arrhythmia (5%), elevated serum glutamate pyruvate transaminase (5%), and abnormal vision (5%). The most common AEs in the fluoxetine group were psychiatric complaints (30%), gastrointestinal complaints (15%), tachycardia (5%), dizziness (5%), and abnormal taste (5%).

Selective Serotonin–Norepinephrine Reuptake Inhibitors

In the study by Allard et al,[29] 62% of patients receiving venlafaxine ER spontaneously reported AEs, compared with 43% of patients receiving citalopram. The most common AEs in the venlafaxine group were dry mouth (12.0%); constipation (6.6%); anxiety, dizziness, stomach pain, vertigo, and urinary tract infection (3.9% each); and tiredness, restlessness, common cold, sweating, and herpes zoster (2.6% each). The most common AEs in the citalopram group were dry mouth (11.0%), dizziness (5.3%), flatulence (5.3%), yawning (4.0%), common cold (4.0%), and dry eyes, feeling hungry, constipation, reduced appetite, virosis, sweating, and influenza (2.7% each).

In the study by de Vasconcelos Cunha et al,[30] the incidence of AEs was 15% in the venlafaxine IR group and 8% in the placebo group. Two patients in the venlafaxine IR group withdrew due to AEs (postural hypotension and visual hallucinations). AEs reported by >10% of patients receiving venlafaxine IR were agitation, tremor, and psychotic symptoms (14% each). In the study by Oslin et al,[31] discontinuation rates due to serious AEs were 33% in the venlafaxine IR group and 12% in the sertraline group; discontinuation rates due to AEs were 15% and 4%, respectively.

In the study by Schatzberg and Roose,[32] rates of discontinuation due to AEs were 27% in the venlafaxine IR group and 9% in the placebo group ($P = 0.002$); there were no significant differences in rates of AE-related discontinuations between fluoxetine (19%) and placebo, or between fluoxetine and venlafaxine. The 2 most frequently reported AEs in the venlafaxine and fluoxetine groups were nausea (45% and 23%, respectively) and headache (26% and 18%). In the study by Gastó et al,[33] only 1 patient (2.9%) in each study arm withdrew due to a serious AE (cutaneous rash in the venlafaxine ER group, severe delirium in the nortriptyline group). Most AEs were mild or moderate. Overall, AEs were reported by 73.5% of the venlafaxine ER group and 82.3% of the nortriptyline group. AEs reported by >10% of patients in the venlafaxine ER group were orthostatic vertigo (52.9%), sweating (41.2%), headache (26.5%), constipation (20.6%), dry mouth (17.6%), nausea (17.6%), insomnia (17.6%), and tremor (11.8%). AEs reported by >10% of patients in the nortriptyline group were dry mouth (67.6%), constipation (41.2%), sweating

(35.3%), impaired visual accommodation (29.4%), impaired urination (26.5%), tremor (26.5%), orthostatic vertigo (23.5%), headache (20.6%), nausea (11.8%), and insomnia (11.8%).

In the study of duloxetine, Raskin et al[34] found no significant difference in discontinuation rates due to AEs between the duloxetine and placebo groups (9.7% and 8.7%, respectively). AEs occurring with a significantly greater frequency in the duloxetine group than the placebo group were dry mouth (14.5% vs 1.9%, respectively; $P < 0.001$), nausea (12.6% vs 3.8%; $P = 0.02$), and diarrhea (8.2% vs 1.9%; $P < 0.05$).

DISCUSSION

In the studies reviewed, both single- and dual-action antidepressants were effective in the treatment of depression in the elderly. The 2 comparative trials of TCAs and SSRIs found no significant difference in efficacy between the comparators.[27,28] Studies comparing venlafaxine with SSRIs in the treatment of depression in the elderly found no significant differences in efficacy between agents.[29,31,32] However, given the lower mean dosing of venlafaxine and the 30:1 serotonin-to-norepinephrine affinity ratio at the doses used, venlafaxine may have inhibited only the reuptake of serotonin in these studies, with minimal effects on norepinephrine reuptake.[36,37] In the single study of duloxetine,[34] this agent was associated with a significant improvement in depression compared with placebo ($P < 0.001$ for reductions in HAM-D and GDS scores), with added benefits in terms of pain ($P < 0.001$) and cognition ($P = 0.013$). To date, there have been no comparative studies of duloxetine and SSRIs.

Depression has significant ramifications in the elderly. The total costs of treating depression in the elderly are increased by the indirect costs associated with an increased morbidity risk (1.5- to 3-fold increase), mortality, and a lifetime suicide risk of ~15%.[38] Each year, almost 10% of elderly patients with depression who attempt suicide die as a result; almost three quarters of these patients had a visit with their primary care physician within the preceding month. The diagnosis of late-life depression is often missed in the primary care setting, resulting in undertreatment of affected individuals.[39] There is evidence that early treatment with medications and psychotherapy can improve symptoms of depression and prevent serious consequences.[40] The 2001 consensus guidelines recommend the use of medication plus psychotherapy as first-line treatment for severe depression in the elderly, with medication alone as an alternative first-line approach.[6] SSRIs (specifically citalopram and sertraline) and venlafaxine ER are recommended as first-line agents, and TCAs, bupropion, and mirtazapine are recommended as second-line agents.[41] The results of 2 of the comparative trials included in the present review suggest that improvement in depression continues over a longer period (8–22 weeks) in elderly patients receiving antidepressant treatment compared with younger adults.[24,29]

Because of variations in dose, duration of treatment, and sample population, it is difficult to compare the results of the studies included in this review. Patients were primarily female in many of the studies, and there were variations in age distribution and medical comorbidities. Because the literature search included only published articles, some studies that have been presented only as conference abstracts may have been omitted, leading to possible publication bias. In addition, some studies may have been missed through the use of only 3 databases and the fact that only a single author extracted the data.

CONCLUSIONS

In this review of recent literature on the treatment of depression in the elderly, TCAs and SSRIs were found to have comparable efficacy. The data did not indicate an added efficacy benefit for venlafaxine compared with SSRIs. In a single trial, duloxetine was associated with a significant difference in efficacy compared with placebo. Thus, the limited data suggest that dual-action agents such as TCAs and SNRIs do not appear to confer any additional efficacy benefits over single-action agents such as SSRIs in the treatment of depression in the elderly.

ACKNOWLEDGMENT

The authors have no potential conflicts of interest to declare.

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