Treatment of depression in late life

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This paper updates the 1996 review of treatment approaches published in the Am J Geriatr Psychiatry *(1996;4[suppl 1]:S51-S65 [see ref 33]) and a chapter in* A Guide to Treatments that Work *(Nathan PE, Gorman JM, eds), Oxford University Press, New York, 1998 [see ref 54]:. The major focus is on psychopharmacology, with attention also to the evidence for the efficacy of psychotherapeutic and somatic approaches.*

The treatment of depression in elderly patients can be differentiated into acute, continuation, and maintenance phases. The treatment goals in each phase vary. The primary goal of acute treatment is to achieve symptom remission. Once a patient has improved symptom-atically, continuation phase treatment attempts to prevent relapse back into the same episode. The goals of maintenance treatment involve sustaining recovery and preventing recurrences. Related treatment objectives include improving longevity and quality of life, enhancing functional capacity, and improving general medical health status. These issues must be considered in selecting treatments and evaluating their outcomes.

Older adults with depression require active treatment, particularly when symptoms interfere with everyday functioning. Research has generally confirmed that standard treatment approaches with proven efficacy in younger populations are likely to be successful when extended to the elderly, and that old age in itself should not be considered a contraindication to their use. However, even though safe and effective treatments are available, nihilistic attitudes on the part of professionals and negative attitudes of the elderly themselves about psychiatric treatment remain barriers to treatment.

Coexisting factors that frequently accompany advanced age—for example, comorbid medical and neurological illness, substance abuse, dementia, and cognitive impairment—are probably greater influences than age itself on the effectiveness of antidepressant treatments in elderly patients. Such comorbidities may interfere with the modes of action of specific treatments. Conversely, effective treatment can improve outcomes of medical treatments and rehabilitation efforts for physical illness in the elderly, and influence survival (ie, depression is a risk factor for mortality). Finally, depression is a risk factor for medical illness, and can complicate its treatment. Thus, there may be serious risks of not treating depression in physically ill elders (Reynolds, this issue, pp 95-99).

Much of the treatment of depression in the elderly occurs within the primary medical health care context, if it occurs at all. Moreover, family members, typically spouses or daughters, provide the bulk of care for older patients with mental disorders, often experiencing considerable stress in the process.

A high proportion of patients experiencing an episode of major depression in late life will have had at least one previous episode, or will have a subsequent recurrence. The literature pertaining to the long-term prevention of a recurrence of depression is discussed elsewhere in this volume (Reynolds, this issue, pp 95-99). These studies indicate that the long-term prevention of new episodes of disorder in elderly patients can be best achieved by maintaining patients on the same dosage of antidepressant medication that was used to treat the acute episode, and by maintaining psychotherapy. Current recommendations are for treatment to be continued for at least 6 months after remission[1] (Agency for Health Care Policy and Research [AHCPR], 1993). Newer information, however, suggests a longer treatment period may be necessary (Reynolds, this issue, pp 95 -97).

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Pharmacological aspects

Pharmacotherapy

Over the years, the amount of data from randomized clinical trials or controlled clinical observation of antidepressant agents in elderly patients has been rather limited, although in recent years there has been a significant increase. Trials in mixed-age adults include very few patients over 60 years of age. Typical outpatient clinical trials for depression in the "elderly" have average ages of only about 65 years and allow patients who are as young as 60 years to be enrolled. The bulk of the patients participating in clinical trials restricted to the elderly are between 60 and 69 years of age, with very few over 75.[2] Consequently, clinical recommendations for the use of antidepressant drugs in elderly patients have been largely derived from experience with young or middle-aged adults.[1,3] Furthermore, the elderly patients who do enter research studies represent an atypical sample of the older population, in that they are volunteers in generally good medical health, thus making it difficult to generalize trial results to those who typically are encountered in primary care. A systematic review of clinical trials for late-life depression, performed in 1991 concluded from over 30 randomized, placebo-controlled, double-blind clinical trials that antidepressants are more effective than placebo in the treatment of acute depression.[4] Approximately 60% of patients showed clinical improvement, although many patients retained significant residual symptomatology. In general, the available antidepressants were considered to be equally effective in the elderly. These clinical trials were only of 3 to 8 weeks duration, assessing only acute response. The medications were largely tricyclic antidepressants (TCAs), trazodone, and bupropion.

Utilization data

Over the last decade there has been a marked transformation in the types of antidepressants used clinically in the elderly. Ten years ago, TCAs were used most commonly. Since the advent and marketing in the US of fluoxetine in 1988, there has been a gradual increase in the uses of selective serotonin reuptake inhibitors (SSRIs) and diminished use of TCAs. In 1998, TCAs accounted for 21% of use in patients 70 years of age or older and SSRIs accounted for 56% (personal communication from Cathryn Clary MD, Pfizer, Inc). The other unique and mixed-action medications such as trazodone, venlafaxine, bupropion, nefazodone, and mirtazapine accounted for the rest, ranging from 6.4% to 3.5% in the order of mention. The three major SSRIs of 1998, fluoxetine, sertraline, and paroxetine, each accounted for approximately 15% to 20% of uses (citalopram was not marketed until the last month of 1998). Amitriptyline was the most commonly used TCA, accounting for 8.5% of uses, and used twice as commonly as nortriptyline (4.4%) or doxepin (3.5%). These data are all the more remarkable when the efficacy evidence base is considered, as it will be below.

Tricyclic antidepressants

Thus the most commonly used TCAs in the elderly are the tertiary amines amitriptyline and doxepin, and the secondary amine nortriptyline, together accounting for 80% of uses. Among the TCAs, the latter two have been preferred by geriatric experts because they have relatively more favorable side-effect profiles than amitriptyline and imipramine, both of which should generally be avoided in elderly patients. Desipramine is less sedating and can be given during the day; nortriptyline causes less orthostatic hypotension than amitriptyline or imipramine. Indeed, it remains surprising that amitriptyline is still commonly prescribed in the USA, apparently in preference to nortriptyline or desipramine, and to trazodone and several newer alternatives.

Nortriptyline has been the most frequently directly studied TCA in elderly patients, involving 300 or more patients in 22 clinical trials.[2,4] It is the only antidepressant to have been directly and extensively studied in very elderly patients (>80 year olds).[2] Results with nortriptyline suggest that the range of plasma concentrations needed for a therapeutic effect is the same in both younger and older patients. However, despite treating patients at plasma levels within a presumed therapeutic "window" (between 50 and 150 ng/mL), significant residual depressive symptoms have been noted in one half of patients in the clinical trials, and specific dosage recommendations cannot be derived from these studies.[5] Clinical practice suggests that effective daily doses in the elderly range from 50 mg to 100 mg, but this should be taken as a guide at best.

There is considerable evidence that clinical response to antidepressant drug therapy depends not only on adequate dose and—in the case of TCAs—blood levels of

medication, but adequate length of treatment as well. There is a general consensus that significant response often occurs later in elderly patients than in younger patients, often after 6 to 12 weeks of therapy.

Medication compliance with TCAs by elderly patients is especially important and difficult to achieve. It has been estimated that 70% of patients fail to take 25% to 50% of their medication.[6] Lack of adherence to instructions results in wide fluctuations in plasma levels, which has been shown to be predictive of poor outcome. Thus, the measurement of plasma blood levels in elderly patients is even more important than in younger patients, both to verify compliance and to confirm that therapeutic drug concentrations have been reached while remaining below toxic levels.

Antidepressant treatment in the 1990s

Many treatment recommendations emanate from the 1991 NIH Consensus Development Conference[7,8] and from the 1993 AHCPR guidelines.[9] At that time, the SSRI fluoxetine had been available for only a few years, and sertraline and paroxetine had not yet been released. Many clinicians favored these medications because of the decreased likelihood of anticholinergic and cardiovascular side effects. Two other SSRIs have been introduced in the USA since then, fluvoxamine in 1996, and citalopram, at the end of 1998. (Fluvoxamine is indicated only for obsessive compulsive disorders in the US, although it is indicated for depression in other parts of the world.) In addition, three non-SSRIs, all with complex neurotransmitter actions, have recently been marketed, nefazodone and venlafaxine, as well as a noradrenergic medication, mirtazapine.

Selective serotonin reuptake inhibitors

To date, there have been at least 20 published clinical trials of the SSRIs marketed in the USA as treatments for depressed elderly patients—nine studies of fluoxetine (Prozac®), eight of paroxetine (Paxil®), and three multicenter trials of sertraline (Zoloft®), comprising nearly 2000 elderly patients. These randomized clinical trials have generally compared the SSRIs with older, more established medications (often with imipramine), rather than with each other or with placebo. The only large-scale placebo-controlled trial that has been published rather surprisingly suggested somewhat lower than

expected efficacy rates for fluoxetine.[10] (Multicenter placebo-controlled trials of paroxetine and sertraline have been completed, but results have not been published.) Over 5- to 12-week study lengths, the various SSRIs (though directly compared in only one randomized clinical trial) have appeared not to be differentially efficacious in treating older patients, but equivalent in efficacy to TCAs. One comparative but nonrandomized study, however, has suggested a lesser efficacy for fluoxetine as compared with nortriptyline in elderly inpatients with severe depression.[11] Overall, when compared with tricyclic antidepressants, the SSRIs are equivalent in efficacy in the elderly, with about 60% of patients responding to treatment, although SSRI-treated patients generally experienced fewer side effects.

Table I provides an overview of selected randomized clinical trials comparing fluoxetine with a number of different antidepressants in elderly patients.[10-21] The trials generally show no marked differences between fluoxetine and the comparator drugs in end-point Hamilton Depression Rating Scale scores (HAM-D). In fluoxetine-treated patients, mean HAM-D scores at the end point generally ranged from about 10 to 16, indicating that the elderly subjects were left with significant residual depressive symptoms. However, the studies were generally too short in duration (5 to 7 weeks) to be conclusive inasmuch as elderly patients may require 6 to 12 weeks of therapy for a full therapeutic effect, and duration of response was not known. For example, patients in the 12-week fluoxetine vs sertraline trials generally had lowest HAM-D scores, regardless of the SSRI used.

Similar results have been observed in short-term paroxetine trials in elderly patients *(Table II)*.[18,19,22-28] As with fluoxetine, trial duration tended to be 6 weeks, HAM-D scores decreased considerably, but residual symptoms of depression remained at the end of the randomized clinical trials, and mean end-point HAM-D scores were generally in the range of 8 to 12.

There are fewer studies with sertraline *(Table III)*,[18-21,29,30] but the duration of treatment is longer, extending from 8 to 12 weeks, the sample size per study is larger, and the relatively higher dosages in these trials, ranging from 50 to 150 mg, were also more realistic. Sertraline was as effective as amitriptyline, nortriptyline, and fluoxetine in these direct comparisons.

Citalopram, an SSRI that has been available in Europe for the last decade, is commonly used in the elderly. There have been, however, relatively few efficacy studies focused

Study	Drugs*	Sample†	Age (years)	Duration (weeks)	Dropout	HAM-D$_{ENDPT}$	Outcome
Altamura et al,[12] 1989	FX 20 mg	14	68	5	14%	14	FX=AMI
	AMI 75 mg	14			28%	10	
	inpatients						
La Pia et al,[13] 1992	FX 20 mg	20	72	6	5%	14	FX=MIA
	MIA 40 mg	20			20%	16	
	outpatients						
Falk et al,[14] 1989	FX 48 mg	14	68	7	21%	10	FX >TRZ
	TRZ 350 mg	13			69%	16	
Fairweather et al,[15] 1993	FX 20 mg	33	70	6	9%	5‡	MADRS, FX=AMI
	AMI 75 mg	33				5‡	FX>AMI attention /
							reaction time
Feighner and Cohn,[16] 1985	FX 60 mg	78	68 (estim)	6	47%	16	FX=DOX
	DOX 125 mg	79			61%	17	
	outpatients						
Tollefson et al,[10] 1995	FX 20 mg	335	68	6	22%	14	FX>PLC, 42% vs 30%
	PLC	336			19%	16	responder rate
	medically ill						
Giakas et al,[17] 1993	FX 40 mg	11	70	8	9%	NA	FX>BUP, 27% vs 0%
	BUP <450 mg	13			46%		responder rate
	medically ill						
Roose et al,[11] 1994	FX	22	73	4-6	18%	16	NT>FX, 67% vs 23%
(not randomized)	NT	42	70		19%	7	responder rate better
	unipolar depression						
	and heart disease						
Schone and Ludwig,[18] 1993	FX 20-40 mg	52	74	6	14%	23	FX=PX, 18% vs 38%
	PX 20-30 mg	54			11%	20	responder rate, FX<PX
	outpatients						for cognition
Newhouse and Richter,[20] 1994;	FX 20-40 mg	119	68	12	22%	11	FX=SR, FX<SR
Linden et al,[21] 1995	SR 50-100 mg	117			17%	11	attention and memory

Table I. Selected clinical trials of fluoxetine in elderly patients with major depression.
*Dosages are expressed as medians or ranges; †Sample size may indicate either completers or number of patients analyzed; ‡Indicates MADRS; AMI, amitriptyline; BUP, bupropion; CMI, clomipramine; DOX, doxepin; FX, fluoxetine; HAM$_{ENDPT}$, Hamilton Depression Rating Scale end point; MADRS, Montgomery-Asberg Depression Rating Scale; MIA, mianserin; NA, not available; NT, nortriptyline; PLC, placebo; PX, paroxetine; SR, sertraline; TRZ, trazodone.

on the elderly. One compared citalopram with amitripty-line finding similar efficacy[31] and the other reported efficacy for citalopram compared with placebo in elderly depressed patients both with and without dementia.[32] When compared with TCAs in standard controlled trials, the SSRIs are equivalent in efficacy in the elderly, with about 60% of patients responding to treatment. Regardless of the antidepressant agent used, the mean HAM-D scores decreased from about 30 to 20 after 6 weeks of treatment, although the fluoxetine-treated patients experienced fewer side effects.[16] A similar comparative response was observed evaluating paroxetine and doxepin.[23] With either compound, the mean HAM-D scores decreased from about 25 to 12 after 6 weeks of treatment. SSRIs may have advantages over TCAs in treating elderly patients, however, because of a more tolerable side-effect profile.[33,34] In particular, in clinical trials, they do not cause orthostasis or cognitive impairment when compared with the other treatment group. Based on clinical experience, they appear to have fewer anticholinergic and cardiovascular side effects (though nausea tends to be a particular problem).[27] Notably, in randomized clinical trials, their tolerability has appeared to be only marginally superior to that of TCAs. In general, the SSRIs as prescribed in these clinical trials do not appear to differ substantially among themselves in side effects; but this depends in part on dose and interindividual differences in pharmacokinetics and sensitivities. Another consideration is the generalizability of the clinical trial experiences to ordinary patients in clinical practices. A pharmacoepidemiological study on antidepressant use in nursing-home patients suggested that SSRI use was associated with falling to an extent equivalent to TCAs.[35] One explanation is that patients in the clinical trials were younger and healthier than those "real-world" patients in nursing homes.

Other antidepressants

Other antidepressants include bupropion, venlafaxine, nefazodone, trazodone, mirtazapine, and tianeptine. They have diverse mechanisms of action, and as a group there is not a considerable amount of published data from elderly populations.

Bupropion may be as effective as TCAs and SSRIs in the treatment of major depression and it is commonly recommended for the elderly, although there is limited

evidence to support its use. Of concern, in two recent studies, one in primary care offices and the other in depressed patients with concomitant medical illnesses, patients tended to be somewhat more intolerant to bupropion than either imipramine or fluoxetine.[17,36] In one placebo-controlled trial in the elderly, although bupropion was effective, it was no more so than imipramine.[36] Older placebo-controlled trials showed mixed results.[37,38] In younger patients, it may cause seizures at high doses and should be given in divided doses. Since clinical trials have excluded patients with cardiovascular disorders, bupropion's apparent margin of safety would not necessarily be applicable to elderly patients with concomitant cardiovascular disease.[36]

Venlafaxine inhibits the reuptake of both serotonin and norepinephrine. It is underresearched in elderly patients and its role for the treatment of depression in late life is uncertain. In clinical trials performed for the Food and Drug Administration's (FDA) registration purposes, elderly patients comprised only 229 out of 2000 patients who received venlafaxine and only a relatively small number of these were administered the drug for more than 1 year. Nevertheless, data from the small subset receiving long-term treatment suggest that tolerability is equivalent to that in younger patients. A trial of venlafaxine could be considered in elderly patients who do not adequately respond to other drug modalities. Venlafaxine has a wide dosage range of 75 to 350 mg/day, administered in divided doses twice or three times daily As with SSRIs, headache, insomnia, and nausea are among the more frequent side effects. Other relatively common reactions include somnolence, dry mouth, dizziness, sweating, and nervousness. Venlafaxine has caused sustained, dose-related increases in systolic blood pressure and diastolic blood pressure, and heart rate (1.1 to 4.5 beats/min).[39,40] Although its effects on blood pressure are not likely to be of clinical importance in an otherwise healthy depressed patient, blood pressure monitoring is needed in patients with preexisting cardiovascular disease or in those receiving relatively high dosages. Recently, a sustained-release preparation has become available that may lessen some of these effects.

Nefazodone is another agent with little published clinical research in the elderly population, although clinical trials have been performed in the elderly, and it thus has an undefined role in the treatment of late-life depres-

Study	Drugs	Sample‡	Age (years)	Duration (weeks)	Dropout	HAM-D$_{ENDPT}$	Outcome
Schone and Ludwig,[18] 1993	PX 20-30 mg	54	74	6	11%	20	PX=FX, 38% vs 18%
	FX 20-40 mg	52			14%	23	responder rate, PX>FX
	outpatients						for cognition
Hutchinson et al,[22] 1992	PX 30 mg	58	72	6	21%	6	PX=AMI, fewer side
	AMI 100 mg	32			34%	6	effects, 76% vs 86%
	outpatients						responder rate
Dunner et al,[23] 1992	PX 23 mg	136	68	6	33%	12	PX(>)DOX, fewer side
(2 studies combined)	DOX 105 mg	135			29%	13	effects
	outpatients						
Guillibert et al,[24] 1988	PX 30 mg	40	69	6	22%	8	PX=CMI, 65% vs 72%
	CMI 75 mg	39			31%	8	responder rate
Rouillon,[25] 1991	PX 30 mg	44	>60	6-9	23%	NA	PX=CMI, 71% vs 65% at
	CMI 75 mg	43			32%	NA	wk 6, 80% at wk 9
	inpatients						
Pelicier and Schaeffer,[26] 1993	PX 20 mg	41	71	5	29%	11	PX=CMI, MADRS scores
	CMI <60 mg	42			24%	13	87% vs 79% responder rate
Geretsegger et al,[19] 1995	PX 23 mg	44	71	6	36%	10	PX=AMI 64% vs 58%
	AMI 110 mg	47			34%	12	responder rate
	inpatients						
Dorman et al,[28] 1990	PX 30 mg	29	>65	6	17%	12	PX(>)MIA
	MIA 60 mg	28			11%	16	
	outpatients						
Roose et al,[27] 1998	PX 20 mg	41	58	6	10%		PX=NT 61% vs 55%
	NT 75 mg	40			35%		responder rate, 18% had
							adverse cardiac events
							compared with 2% on PX

Table II. Selected randomized clinical trials of paroxetine in elderly patients.
Symbols and abbreviations: see *Table I.*

Study	Drugs	Sample	Age (years)	Duration (weeks)	Dropout	HAM-D$_{ENDPT}$	Outcome
Cohn et al,[29] 1990	SR 116 mg*	161	70	8	49%	10	SR=AMI, 69% vs 62%
	AMI 88 mg	80			51%	11	responder rate
McEntee et al,[30] 1995	SR 50-150 mg	104	68	12	6%	10	SR=NT, 83% vs 80%
	NT 25-100 mg	104			12%	11	responder rate SR>NT for
							attention and memory
Newhouse and Richter,[20] 1994;	SR 50-100 mg	117	68	12	17%	11	SR=FX, SR>FX for
Linden et al,[21] 1995	FX 20-40 mg	119			22%	11	attention and memory

Table III. Selected randomized clinical trials of sertraline in elderly patients.
Symbols and abbreviations: see *Table I.*

sion. It has a dosage range of 300 to 500 mg/day, which is administered in divided doses, twice daily. Although associated with dose-related cognitive and psychomotor effects, the drug seems to be relatively well tolerated and relatively safe in overdosage. Ideally, the pharmaceutical company will release results of their trials.

Mirtazapine, in a randomized, double-blind trial in elderly depressed patients, was somewhat less effective than amitriptyline,[41] but was somewhat more effective than trazodone or placebo in another 6-week trial.[42] In the latter study, both treatments were associated with a higher frequency of somnolence and dry mouth as compared with placebo. Trazodone also had higher frequencies of dizziness and blurred vision than placebo.[42]

Tianeptine is an enhancer of presynaptic serotonin uptake and has been marketed in Europe over the last decade. One randomized trial including 315 elderly outpatients showed equal tolerability and efficacy to mianserin.[43]

Efficacy vs effectiveness

Although TCAs and SSRIs have similar *efficacy* in elderly patients, the *effectiveness* of SSRIs is likely to be somewhat better. Efficacy is the measure of a medication's expected action when given to a defined population for a defined problem, regardless of other considerations such as tolerability, side effects, or dropouts. Effectiveness is efficacy *plus* a favorable outcome, with fewer complications under conditions faced by the

community-based practitioners. This distinction is important since a larger percentage of primary care physicians than psychiatrists treat depression in the elderly and there are noteworthy differences between the two types of practice. Psychiatrists see more patients who are able to self-pay for service. Their patients are thus likely to be more highly motivated, and are also more likely to receive psychotherapy. Also psychiatrists may be expected to help a patient better cope with side effects. By contrast, primary care physicians are less likely to require return appointments or follow up on the depression, and spend less time with their patients. This differential pattern of patient care can lead to a different pattern of prescribing and a differential pattern of effectiveness.[44]

A significant measure of effectiveness in clinical trials is the dropout rate. *Tables I to III* provide an overview of dropout rates in many trials of SSRIs versus TCAs and other active/control medications. Dropout rates for patients on SSRIs were generally one third to one half that of groups of patients treated with TCAs, although there are notable exceptions.

This finding is not surprising when one considers the benefit/side-effect profile of the TCAs. For example, nortriptyline may be favored because of predictable pharmacokinetics and a relative lack of orthostatic hypotension. However, important disadvantages it shares with other members of the TCA class include persistent psychomotor and cognitive changes, as well as anticholinergic effects. These undesirable secondary actions may contribute to a high variability in patient acceptance.

In addition, certain adverse effects of TCA therapy in

general can be particularly hazardous in the elderly. These include orthostatic hypotension, sedation, and cardiac toxicity. It has been suggested that TCAs, such as type II (quinidine-like) antiarrhythmics, may actually be proarrhythmic in patients who have ischemic heart disease, with potentially fatal outcome.[45]

The improved tolerability of SSRIs is based on fewer anticholinergic effects, little or no influence on cognition in recommended doses, and no cardiovascular adverse effects such as orthostatic hypotension, proarrhythmia, or increased heart rate. Common complaints linked to these agents include nausea, diarrhea, insomnia, headache, agitation, and anxiety. Based on available data, it is not possible to determine whether or not the elderly are more sensitive than younger populations to these more frequent side effects.[2] It should also be noted that SSRIs are metabolized in the liver and inhibit the drug metabolizing enzyme cytochrome P-450, particularly isoenzyme CYP2D6, but others as well. The difference among SSRIs in this respect is probably of limited importance despite their heterogeneous metabolism. But this discussion is beyond the scope of this paper. It is widely acknowledged that a serotonin syndrome (excitation tremor, pyrexia) or a potentially fatal drug-drug interaction may occur if SSRIs are combined with MAOIs or L-tryptophan, or other drugs that might raise serotonin levels.

Under its Evidence-Based Practice Program to guide clinical practice, the AHCPR reviewed newer antidepressants. With regard to older adults, and consistent with the above, dropouts overall and due to adverse effects do not differ significantly between older and newer antidepressants.[46] In mixed-aged adults (data from older adults not being available), subjects discontinued treatment at similar rates for newer and older antidepressants due to lack of efficacy, adverse effects, or other reasons. However, about 4% fewer patients taking SSRIs discontinued treatment due to adverse effects compared with patients taking TCAs. Compared with TCAs, SSRIs had higher rate differences (7% to 10%) of diarrhea, nausea, and insomnia, and a slight increase in headaches. TCAs had higher rate differences of dry mouth (30%), constipation (12%), dizziness (11%), blurred vision, and tremors (4%). Of particular concern in the elderly, several uncommon (<1%), but serious, adverse effects were associated with the SSRIs, including bradycardia, bleeding, granulocytopenia, seizures, hyponatremia, hepatotoxicity, serotonin syndrome, extrapyramidal effects, and mania.

Psychosocial therapy

Psychosocial treatments have an essential role in the treatment of late-life depression because of the broad range of functional and social consequences of depression in the elderly. Antidepressant treatments or electroconvulsive therapy (ECT) alone do not resolve many of the problems associated with geriatric depression, including lack of social support, medical illnesses, and significant and continuing adverse life events. Further, some patients strongly prefer non-biologic interventions, while others are not suitable candidates for biologic interventions because of side effects, concomitant illnesses, or other circumstances. There are at least 8 randomized controlled trials indicating that psychosocial interventions are efficacious in treating major depression in the elderly (Table IV).[47-54] Other controlled studies demonstrate the use of psychosocial approaches in elderly samples of mixed depression subtypes, including mild depression or depressive symptoms. The treatments studied include cognitive-behavioral, brief psychodynamic, interpersonal, reminiscence/life review, and psychoeducational modalities. For extensive reviews, see other sources.[55,56] (Reminiscence and life-review therapies, relatively specific to the elderly, emphasize the recall and recounting of past life experiences, sometimes with reinterpretation of their meanings or reworking of issues previously left unresolved.[57])

In general, efficacy appears comparable for cognitive-behavioral therapy and brief psychodynamic treatments, showing significantly reduced depression over 6 weeks, relative to a delayed-treatment control condition. Interpersonal therapy has not been directly compared with other psychosocial approaches, but generally shows equivalent responses.[51]

The evidence suggests that reminiscence therapy or psychoeducational interventions show efficacy in reducing depressive symptoms and dysphoric affect in elders with subclinical (or possibly dysthymic) forms of depression, but their efficacy in treating older adults who already manifest clinically diagnosable depression has not been adequately established.

Psychosocial treatments—generally variants of cognitive-behavioral therapy[58] or interpersonal therapy[59]—with depressed older adults who had concomitant medical illness or physical impairments, such as nursing-home residents, generally show some antidepres-

Study	Comparison conditions	Sample size	Age* (years)	Gender (% female)	Duration (weeks)	Sessions	Baseline Hamilton
Arean et al,[47] 1993	Problem-solving	75	66	75	12	12	24
	Reminiscence						
	Waiting List Control						
Beutler et al,[48] 1987	CBT + pill placebo	56	71	55	20	20	21
	CBT + alprazolam						
	Pill placebo						
	Alprazolam						
Brand and Clingempeel,[49] 1992	Behavioral therapy	53	72	89	2	8	24
	+ standard hospital program						
	Standard hospital program						
Gallagher and Thompson,[50] 1982	Behavioral	30	68	77	12	16	18
	Cognitive						
	Psychodynamic						
Sloane et al, [51] 1985	IPT	24	64	53	16	16	26
	Nortriptyline						
	Pill placebo						
Steuer et al,[52] 1984	CBT	33	66	79	36	46	20
	Psychodynamic						
Thompson et al,[53] 1991	Behavioral	91	67	67	12-16	16-20	19
	Cognitive						
	Psychodynamic						
	Waiting List Control						
Thompson et al,[54] 1991	CBT	102	67	67	12-16	16-20	19
	Desipramine						
	CBT + desipramine						

Table IV. Controlled clinical trials of psychosocial interventions with elderly patients with major depression.
*Approximate mean or median age; CBT, cognitive-behavioral therapy; IPT, interpersonal therapy.

sant efficacy, but often with limitations in the effect or duration of the benefit.

In summary, various forms of psychotherapy (particularly cognitive-behavioral, psychodynamic, and interpersonal approaches) have demonstrated efficacy in decreasing depression in older adults, and the various psychotherapies studied have generally proven equivalent in their effects. These findings have been supported by a meta-analysis of 17 published studies of psychosocial treatments for depressed elderly patients, including cognitive, psychodynamic, reminiscence, and eclectic approaches.[60] Overall, these treatments are reliably more effective than no-treatment conditions in reducing depression, the short-term effect size comparing favorably with the effect sizes for psychosocial treatments with adults of younger ages. There is no clear advantage, however, for group versus individual therapy or for any particular treatment approach. In general, the findings regarding treatment outcomes are comparable to those found in psychotherapy research with younger adults.

Pharmacological aspects

Long-term maintenance approaches are discussed elsewhere[61] and in this issue (Reynolds, pp 95-97).

Electroconvulsive therapy in the elderly

ECT remains the most effective treatment for severe major depression, despite its controversy. It is used particularly for patients with severe depression, delusional depression, hallucinations and other psychotic features, severe psychomotor slowing, catatonic stupor, and marked or persistent suicidality. ECT should also be considered for moderately or severely depressed patients who have not responded to adequate trials of medications or who have suffered from intolerable medication side effects. Remission rates of 80% have been achieved for severely depressed patients in recent studies.[62] Unilateral, nondominant hemisphere, stimulus-titration methods are effective, reduce adverse side effects such as post-ECT confusion and cognitive impairment, and tend to be used initially.[63,64] Absolute contraindications for ECT are few, the most notable being increased intracranial pressure. With appropriate precautions, ECT can be safely administered to patients with concurrent medical illnesses. Conditions that increase risk of complications with ECT are recent myocardial infarction and severe hypertension. The most common post-ECT problems for patients over age 85 years appear to be delirium or confusion (32%), transient hypertension (67%), and reversible cardiac ectopy during treatment (18%).[65]

Although acute remission or response rates are high, patients successfully completing a course of ECT may be at risk for relapse and should be placed on maintenance antidepressant. Although controlled clinical trials have not been completed, many clinicians believe that maintenance ECT can be an effective strategy for preventing early relapse in patients who have been refractory to or intolerant of medication. Maintenance ECT is generally given as an outpatient procedure every month.

Conclusions: from 1991 to 1999

Despite many more clinical trials involving the use of newer antidepressant compounds, there is far too little research that addresses the fundamental issues of effectiveness and practical application in a variety of clinical settings. The effectiveness of SSRIs in primary practice is likely to be better than that of the TCAs from the perspective of tolerability and frequency of visits. Although prescribing data suggest that practitioners are convinced about the effectiveness of newer agents, there are too few clinical trials, however, that provide head-to-head comparisons of the newer agents in elderly populations. Only limited generalizations can be made from the clinical trials' data, and treatment recommendations are still based upon young or middle-aged adults or relatively healthier (younger, ages 60 to 69) older outpatients who do not reflect the heterogeneity of patients with late-life depression (as exemplified by the AHCPR evaluation of new antidepressants). The same can be said for psychosocial treatments. Nevertheless, for the reasons discussed above, SSRIs currently are generally considered antidepressants of first choice among the elderly, at least over the short term.

Much more needs to be done to evaluate clinical and real-world outcomes, not just rating scale end points. There is a need for disease management protocols that are based upon a solid foundation of research in late-life depression. There is a dearth of practical inpatient and outpatient guidelines and treatment recommendations that take into account the wide interpatient variation and concomitant medications, or contain clinically meaningful definitions for depression and treatment response. In conclusion, new approaches to clinical research are needed.

The AHCPR guidelines, NIH Consensus Conference, and NIH Update on treating "geriatric depression" all stress that the efficacy of the various treatments for depression in the elderly is, by and large, equivalent to that found in adults in general. Differences, however, in dealing with the elderly involve the recognition of depression, overcoming barriers to care, and the particular practical problems discussed above. For example, the consequences of unrecognized and untreated depression in the elderly include increased health services utilization, longer hospital stays, poor treatment compliance, and increased morbidity and mortality from medical illness and suicide. The costs of treatment are relatively modest and can be minimized by careful monitoring of the patient's clinical status.

Other points to be made include: (i) major depressive disorder in late life is a treatable illness; (ii) evidence for the specific efficacy of medication is based on randomized placebo-controlled trials; (iii) evidence exists for the efficacy of psychotherapy alone as a

treatment for less severely ill, nonpsychotic outpatients, though this area remains understudied; (iv) electroconvulsive therapy appears to be effective in geriatric patients with severe or psychotic major depressive; (v) evidence for or against the efficacy of

combined acute phase treatment with both psychotherapy and medication is generally lacking in geriatric patients, but combined therapy is clearly a clinical advantage; and (vi) the utility of maintenance phase medication is suggested by a few studies. ❏

Tratamiento de la depresion de sujetos de edad avanzada

El presente artículo actualiza la revisión de 1996 sobre los enfoques terapéuticos, publicada en el Am J Geriatr Psychiatry *1996;4 (suppl 1):S51-65 (ver referencia 33) y el capítulo de A* Guide to Treatments that Work *(Nathan PF, Gorman JM, eds), Oxford University Press, New York, 1998 (ver referencia 54). Se centra el interés en la psicofarmacología, poniendo énfasis también en las pruebas existentes de la eficacia de la psicoterapia y de los enfoques somáticos.*

Traitement de la dépression du sujet âgé

*Cet article est une mise à jour d'une revue des approches thérapeutiques de la dépression du sujet âgé, publiée en 1996 dans l'*Am J Geriatr Psychiatry *1996; 4 (suppl 1): S51-65 (voir référence 33) et dans le chapitre d'un livre publié en 1998, consacré aux traitements efficaces (A* Guide to Treatments that work. *Nathan PE, Gorman JM, eds, Oxford University Press, New York, 1998) (voir référence 54). L'accent est tout particulièrement mis sur la psychopharmacologie, mais l'attention se porte également sur les données qui établissent l'efficacité de la psychothérapie et de l'approche somatique.*

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