The Effectiveness of Antidepressants in Elderly Depressed Outpatients: A Prospective Case Series Study

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Background: This study examined the effectiveness of antidepressants in a group of elderly depressed outpatients by assessing depression prevalence and recording adverse events over time.

Method: A prospective practice-based observational study (1991–1994) included consecutive outpatients at least 65 years of age with a DSM-III-R diagnosis of major affective disorder and who were prescribed antidepressant medications. Depressive symptoms were examined over time (stage 1 = 0 to 2 months; stage 2 = 2 to 6 months; stage 3 = 6 months to 2 years) with the Montgomery-Asberg Depression Rating Scale (MADRS). The cutoff scores of MADRS < 18 and MADRS ≥ 18 were used in survival statistics. Adverse events were recorded systematically.

Results: A total of 213 patients were seen over 2677 visits (mean ± SD age = 75.5 ± 6.1 years). MADRS scores for 85.8% of patients declined to below 18 within the first 2 months of antidepressant treatment. MADRS scores were above 18 for 37.3% of patients after 6 months and for 37.1% after 2 years. The mean time to decline in MADRS scores to below 18 in stage 1 was 36.1 days, and there was a significant difference between the antidepressant classes (log rank = 8.3, df = 3, p = .04), with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)/reversible inhibitors of monoamine oxidase A (RIMAs) having shorter times to response. The mean time to reach scores above cutoff during stage 2 was 144.3 days (log rank = 5.7, df = 3, p = .13) and during stage 3, 538.6 days (log rank = 9.8, df = 3, p = .02). Patients receiving TCAs and MAOIs/RIMAs had longer durations of MADRS scores below cutoff during stage 3 than those taking atypical antidepressants and selective serotonin reuptake inhibitors. All antidepressant classes reported similar adverse event profiles.

Conclusion: This study systematically examined antidepressant effectiveness in a prospective design. TCAs and MAOIs/RIMAs were shown to be superior in effectiveness during 2 of the 3 treatment stages.

(J Clin Psychiatry 1999;60:690–697)

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Antidepressants are widely prescribed to elderly depressed patients. Despite widespread use, there is limited information on their effects in the aged. Treatment recommendations for the elderly are often extrapolated from adult nonelderly patients. Relatively few controlled comparative trials of antidepressants have been conducted in the elderly.[1–3] A recent detailed meta-analysis showed no significant differences with respect to efficacy, safety, and dropouts between tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), reversible inhibitors of monoamine oxidase A (RIMAs), and atypical antidepressants.[1] In view of possible phenomenological and etiologic differences between early-onset depression and depression in late life, as well as age-related pharmacokinetic and pharmacodynamic changes, such extrapolation may not be valid.[3] Given the scope of depression, coupled with the paucity of knowledge, there is a need to determine how well antidepressants work in this population.

Examining how well antidepressants work in the elderly requires a comprehensive approach with information on treatment efficacy and effectiveness. A study of drug efficacy is "a study of whether, under ideal conditions, a drug has the ability to bring about the effect intended when prescribing it."[4(p695)] In contrast, a study of drug effectiveness is "a study of whether, in the usual clinical setting, a drug in fact achieves the effect intended when prescribing it."[4(p695)] Efficacy is typically measured in experimental environments that are rigidly controlled, whereas effective-

ness studies examine how well medications work in usual-use situations or clinical practice. Effectiveness is measured with observational or pharmacoepidemiologic studies, which are not bound by the constraints of controlled clinical trials. Advantages of observational studies include the ability to study populations typically excluded from clinical trials, for longer durations of time and in a variety of clinical settings. This is particularly advantageous when studying elderly populations, many of whom would be excluded from controlled clinical trials because of comorbid medical conditions and concomitant medication use.

The objective of this study was to evaluate the effectiveness of antidepressants in elderly depressed outpatients using a prospective practice-based pharmacoepidemiologic model.

METHOD

The practice-based population consisted of a group of consecutive outpatient clinic patients. Patients 65 years of age or older meeting DSM-III-R criteria for major depression were included.[5] Patients with a diagnosis of bipolar affective disorder were excluded. Diagnosis was made clinically by academic geriatric psychiatrists (N.H., I.L.S., K.I.S.). Eligible patients were prescribed any antidepressant medication and could be at any stage in therapy. All patients signed informed consent statements approved by the Sunnybrook Health Science Centre research ethics committee before entering the study.

The study was conducted in the geriatric psychiatry outpatient clinic of Sunnybrook Health Science Centre, a University of Toronto teaching hospital, from May 1991 through December 1994. The clinic serves approximately 200 active patients and is staffed by a multidisciplinary team including 3 geriatric psychiatrists, a pharmacist, a social worker, and a nurse. The clinic provides primary psychiatric care to a well-defined geographical catchment area as well as tertiary care to the larger metropolitan area. Most of the patients in the clinic have affective disorders and are treated with antidepressants. Patients were seen on a weekly to annual basis by their attending psychiatrist. The 3 psychiatrists, with 3 individual practices, are of similar ages and have similar educational and clinical backgrounds.

Historical and demographic data were obtained from medical records and by interviews with the patient, available family members, and the attending psychiatrist. Patients were interviewed at each clinic visit. Prior to each appointment, a record of the prescribed antidepressant pharmacotherapy including name of drug, dose, duration on dose, duration of treatment with drug, concurrent drug use, and any comorbid illness was obtained from the subject's medical record. This information was later verified with the patient and the physician at the time of the interview. Physicians prescribed any medications that they thought were reasonable. Antidepressants were categorized as TCAs, SSRIs, monoamine oxidase inhibitors (MAOIs)/RIMAs, and atypical antidepressants. Concomitant medications were classified according to the Anatomical Therapeutic Chemical Classification System.[6] Comorbid illnesses were classified according to the Cumulative Illness Rating Scale.[7] Exposure to electroconvulsive therapy was also recorded.

Patients attended the clinic for their scheduled visit, at which time outcome measures were completed. The main outcome measure in this study, the Montgomery-Asberg Depression Rating Scale (MADRS),[8] was completed by the treating psychiatrist. Adverse events were recorded if the symptoms had not been present before antidepressant treatment or had been present but to a lesser degree. A list of adverse events frequently encountered with antidepressants was used to aid in eliciting those events that were not self-reported.

As patients were seen over time, the sample was stratified according to antidepressant class and treatment stage. Treatment stage was categorized as stage 1 (0 to 2 months), stage 2 (2 to 6 months), and stage 3 (6 months to 2 years). Patients were categorized into treatment stages and were followed prospectively until there was a decline below or increase above a predetermined MADRS score. A dichotomous response was necessary for the survival analysis. The primary analysis examined the time to decline in MADRS score to < 18 (stage 1) or increase to ≥ 18 (stages 2 and 3); a similar measurement was made in the secondary analysis, except the cutoff MADRS scores were adjusted to < 8 (stage 1) and ≥ 8 (stages 2 and 3).[9] Kaplan-Meier survival statistics were conducted for each treatment stage for each antidepressant class.

RESULTS

The study consisted of a total 2677 visit records; 444 records (16.6%) did not contain study information. Of the records that contained study information, 62.9% (N = 1404) of visits were fully completed (i.e., physician and patient section), 30.7% (N = 685) had only the physician section completed, 5.6% (N = 126) had only the patient section completed, and the remainder were not completed for other reasons. There were a total of 213 patients. The majority of study subjects were taking concomitant medications (89.2%; N = 190). The majority of patients had comorbid illnesses (88.3%; N = 188). Demographic information for all patients at the initial study contact is summarized in Table 1.

At the initial study visit, the most commonly prescribed antidepressant was doxepin (24.9%), followed by nortriptyline (20.2%) and tranylcypromine (10.3%). Data for antidepressant drugs and doses are summarized in Table 2. At the initial study visit, the mean antidepressant duration of treatment was 877.3 ± 1112.0 days (range,

Table 1. Demographic Information for Observational Population at Initial Study Visit[a]

Variable	Value Total
Age, y, mean ± SD[b]	75.5 ± 6.1
Range, y	65–90
Gender, female[b]	160 (75.1)
Marital status[b]	
Single	23 (10.8)
Married	89 (41.8)
Widowed	87 (40.8)
Other	14 (6.6)
Housing[b]	
Alone	89 (41.8)
Spouse	87 (40.8)
Family	14 (6.6)
Other	23 (10.8)
Prior hospitalizations, yes[b]	116 (54.5)
Electroconvulsive therapy, yes[b]	67 (31.5)
Comorbid illnesses, yes[c]	188 (88.3)
Cardiac	49 (26.1)
Vascular	69 (36.7)
Respiratory	21 (11.2)
Eye, ear, nose, and throat	50 (26.6)
Upper gastrointestinal	40 (21.3)
Lower gastrointestinal	29 (15.4)
Hepatic	2 (1.1)
Renal	3 (1.6)
Other genitourinary	43 (22.9)
Musculoskeletal-integumentary	68 (36.2)
Neurologic	53 (28.2)
Endocrine	60 (31.9)
Concomitant medications, yes[d]	190 (89.2)
Alimentary	72 (37.9)
Blood and blood-forming organ agents	21 (11.1)
Cardiovascular	90 (47.4)
Dermatologic	1 (0.5)
Genitourinary	11 (5.8)
Systemic hormonal, excluding sex hormones	41 (21.6)
General anti-infective agents	3 (1.6)
Antineoplastic	11 (5.8)
Musculoskeletal integumentary	26 (13.7)
Nervous system	164 (86.3)
Respiratory	16 (8.4)
Sensory	9 (4.7)
Family with positive psychiatric history, yes	88 (41.3)

[a]All values shown as N (%) unless otherwise specified.
[b]Total N = 213.
[c]Percentages of patients with individual illnesses are of the total number of patients with an illness.
[d]Percentages of patients receiving individual medications are of the total number of patients receiving any medication.

Table 2. Antidepressant Doses at Initial Study Visit[a]

Antidepressant Class	N (%)[b]	Study Dose, mg/d Mean	SD	Range	Maximum Prescribed Dose, mg/d
TCAs					
Amitriptyline	10 (4.7)	44.0	29.8	10–100	100
Clomipramine	1 (0.5)	30.0	0.0		100
Desipramine	11 (5.2)	70.0	52.7	20–175	175
Doxepin	53 (24.9)	64.3	43.1	10–200	200
Imipramine	8 (3.8)	56.3	22.2	25–100	200
Nortriptyline	43 (20.2)	39.9	26.8	10–125	150
Trimipramine	2 (0.9)	137.5	17.7	125–150	150
SSRIs					
Fluoxetine	12 (5.6)	13.1	6.3	4.9–20	40
Fluvoxamine	5 (2.3)	90.0	41.8	50–150	350
Paroxetine	2 (0.9)	10.0	0.0		30
Sertraline	11 (5.2)	54.5	15.1	50–100	600
MAOIs/RIMAs					
Moclobemide	6 (2.8)	279.2	95.4	200–450	750
Phenelzine	8 (3.8)	31.9	12.5	15–45	60
Tranylcypromine	22 (10.3)	21.8	10.5	10–40	60
Atypical					
Bupropion	10 (4.7)	210.0	92.2	75–300	450
Nefazodone	1 (0.5)	100.0	0.0		100
Trazodone	3 (1.4)	133.3	76.4	50–200	300
Other					
Lithium	63 (29.6)	319.4	122.9	150–750	750

[a]Patients could have been taking more than one antidepressant agent.
Abbreviations: MAOIs = monoamine oxidase inhibitors, RIMAs = reversible inhibitors of monoamine oxidase A, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.
[b]Total N = 213 patients.

3–4566 days), with half of the patients using antidepressants for more than 324 days. The most commonly prescribed antidepressants from 1991 to 1994 were doxepin and nortriptyline. The most common new prescriptions during the study period were sertraline and moclobemide.

For the primary analysis, there were 190 patients in stage 1 (14.2% received an atypical antidepressant, 21.6% an MAOI/RIMA, 33.2% an SSRI, and 31.1% a TCA). MADRS scores declined to below 18 during the first 2 months for 85.8% of patients. A total of 14.2% were prescribed lithium augmentation. The mean ± SD baseline MADRS score for patients in all drug treatment groups was 19.9 ± 8.6 (atypical antidepressants: 19.9 ± 8.6; MAOIs/RIMAs: 17.5 ± 9.2; SSRIs: 18.7 ± 10.5; TCAs: 14.8 ± 8.5). The mean time for MADRS scores to decline to below cutoff was 36.1 (95% confidence interval [CI] = 33.3 to 38.9) days overall, 41.9 (95% CI = 34.2 to 49.5) days for patients receiving an atypical antidepressant, 35.5 (95% CI = 29.4 to 41.7) days for those receiving an MAOI/RIMA, 38.9 (95% CI = 34.3 to 43.5) days for those receiving an SSRI, and 31.3 (95% CI = 26.6 to 31.6) days for those receiving a TCA. There was a significant difference between the classes (log rank statistic = 8.3, df = 3, p = .04; Figure 1). The mean ± SD final MADRS score for patients in all drug treatment groups was 16.0 ± 9.3 (atypical antidepressants: 18.8 ± 9.3; MAOIs/RIMAs: 16.7 ± 9.2; SSRIs: 16.7 ± 10.1; TCAs: 13.8 ± 8.1).

There were 158 patients in stage 2 (2- to 6-month study duration; 12.0% received an atypical antidepressant, 23.4% an MAOI/RIMA, 27.8% an SSRI, and 36.7% a TCA). MADRS scores increased to 18 or higher for 37.3% of patients. A total of 19.0% were prescribed lithium. The mean ± SD baseline MADRS score for patients in all drug treatment groups was 12.9 ± 8.7 (atypical antidepressants: 14.6 ± 8.1; MAOIs/RIMAs: 12.8 ± 9.0; SSRIs: 12.1 ± 8.1; TCAs: 13.2 ± 9.4). The mean time for MADRS scores to increase to 18 or higher was 144.3 (95% CI = 137.5 to 151.1) days overall, 132.5 (95% CI = 112.9 to 152.1) days for patients receiving an atypical antidepressant, 135.6 (95% CI = 120.5 to 150.2) days

Figure 1. Survival Analysis for Stage 1 (0–2 months)

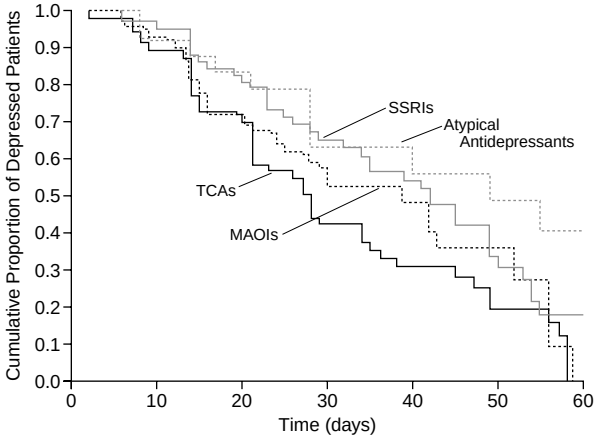
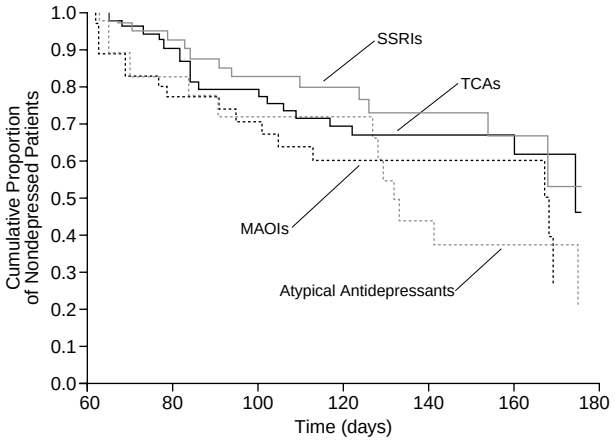


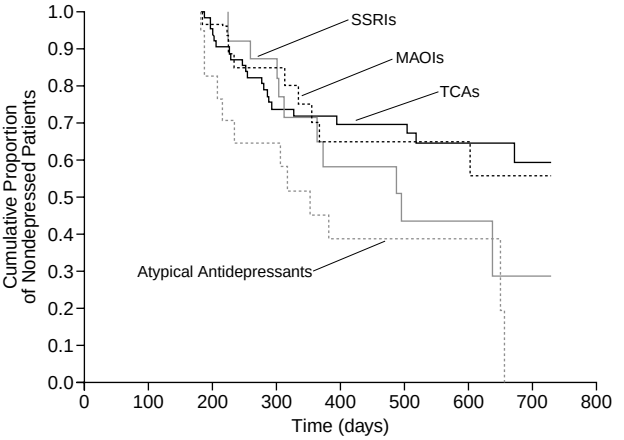
Figure 2. Survival Analysis for Stage 2 (2–6 months)



for those receiving an MAOI/RIMA, 152.7 (95% CI = 141.0 to 164.5) days for those receiving an SSRI, and 146.9 (95% CI = 136.1 to 157.7) days for those receiving a TCA. There was no significant difference between the 4 classes (log rank test = 5.7, df = 3, p = .13; Figure 2). The mean ± SD final MADRS score for patients in all drug treatment groups was 11.7 ± 8.7 (atypical antidepressants: 15.2 ± 8.0; MAOIs/RIMAs: 11.8 ± 9.9; SSRIs: 10.0 ± 6.9; TCAs: 12.1 ± 9.1).

There were 143 patients in the antidepressant-only group (12.6% received an atypical antidepressant, 18.9% an MAOI/RIMA, 21.0% an SSRI, and 47.6% a TCA) in stage 3 (6-month to 2-year study duration). MADRS scores increased to 18 or higher for 37.1% of patients. A total of 25.9% were prescribed lithium augmentation. The mean ± SD MADRS score for patients in all drug treatment groups was 10.7 ± 0.8 (atypical antidepressants: 13.6 ± 10.7; MAOIs/RIMAs: 10.4 ± 9.3; SSRIs: 11.2 ± 8.9; TCAs: 9.9 ± 8.4). The mean time for MADRS scores to increase to 18 or higher was 538.6 (95% CI = 499.7 to 577.4) days overall, 414.6 (95% CI = 313.8 to 515.4) days for patients receiving an atypical antidepressant, 558.6 (95% CI = 474.5 to 642.8) days for those receiving an MAOI/RIMA, 503.0 (95% CI = 416.5 to 589.5) days for those receiving an SSRI, and 572.2 (95% CI = 517.8 to 626.6) days for those receiving a TCA. There was a significant difference between the 4 classes (log rank test = 9.8, df = 3, p = .02; Figure 3). The mean ± SD final MADRS score for patients in all drug treatment groups was 11.9 ± 9.1 (atypical antidepressants: 17.8 ± 8.9; MAOIs/RIMAs: 9.7 ± 9.2; SSRIs: 12.8 ± 9.4; TCAs: 11.0 ± 8.4).

Figure 3. Survival Analysis for Stage 3 (6–24 months)



For the secondary analysis, MADRS scores declined to below 8 for 21.1% of patients during stage 1. A total of 14.7% were prescribed augmentation with lithium. The mean ± SD baseline MADRS scores were the same as for the primary analysis. The mean overall time to decline to below cutoff was 51.4 (95% CI = 49.1 to 53.8) days, 54.4 (95% CI = 50.0 to 58.7) days for patients receiving an atypical antidepressant, 50.1 (95% CI = 44.6 to 55.6) days for those receiving an MAOI/RIMA, 51.9 (95% CI = 47.9 to 55.8) days for those receiving an SSRI, and 49.2 (95% CI = 45.0 to 53.4) days for those receiving a TCA (log rank test = 2.1, df = 3, p = .55). The mean ± SD final MADRS score for patients in all drug treatment groups was 16.0 ± 9.6 (atypical antidepressants: 19.7 ± 9.5; MAOIs/RIMAs: 16.6 ± 9.4; SSRIs: 16.9 ± 10.3; TCAs: 13.1 ± 8.6).

In stage 2, MADRS scores increased to 8 or higher for 71.5% of patients. The mean overall time to increase to above cutoff for patients in all drug treatment groups was 112.8 (95% CI = 106.4 to 119.2) days, 107.0 (95% CI = 90.0 to 124.0) days for those receiving an atypical an-

tidepressant, 114.6 (95% CI = 100.0 to 129.1) days for those receiving an MAOI/RIMA, 107.6 (95% CI = 96.3 to 118.9) days for those receiving an SSRI, and 117.0 (95% CI = 106.7 to 127.0) days for those receiving a TCA. There was no significant difference between the 4 classes (log rank test = 2.04, df = 3, p = .57). The mean ± SD final MADRS score for all drugs was 11.9 ± 8.8 (atypical antidepressants: 11.8 ± 7.7; MAOIs/RIMAs: 12.4 ± 10.7; SSRIs: 10.8 ± 7.4; TCAs: 12.4 ± 8.9).

In stage 3, MADRS scores increased to 8 or higher for 71.0% of patients. The overall mean time to increase in MADRS score to 8 or above was 401.9 (95% CI = 366.9 to 436.9) days. For patients receiving an atypical antidepressant, the time was 454.5 (95% CI = 325.1 to 583.8) days; for those receiving an MAOI/RIMA, 595.9 (95% CI = 501.2 to 690.5) days; for those receiving an SSRI, 487.8 (95% CI = 389.7 to 586.0) days; and for those receiving a TCA, 619.4 (95% CI = 566.3 to 672.6) days. There was a significant difference between the 4 classes (log rank test = 9.6, df = 3, p = .02). The mean ± SD final MADRS score for patients in all drug treatment groups was 11.5 ± 8.2 (atypical antidepressants: 15.7 ± 9.5; MAOIs/RIMAs: 10.4 ± 8.6; SSRIs: 12.5 ± 8.3; TCAs: 10.6 ± 7.4).

Adverse events were reported according to visits, not per patient, because patients may have had more than one visit. Information on adverse events was not available for 1179 visits (52.8%). When the data regarding adverse events were obtainable, adverse events were reported for 85 (66.4%) of 128 visits for patients receiving an atypical antidepressant, 206 (67.3%) of 306 visits for those receiving an MAOI/RIMA, 214 (71.1%) of 301 visits for those receiving an SSRI, and 616 (85.3%) of 722 visits for those receiving a TCA ($\chi^2 = 56.2$, df = 3, p < .001). For those visits where adverse events were reported, there was a mean ± SD of 2.6 ± 1.7 adverse events per visit reported (range, 1–11). The most common adverse events per visit for each antidepressant class are listed in Table 3.

Table 3. Frequency of Adverse Events for Study Visits

Adverse Event	TCAs (%)[a] (Total No. = 614)	SSRIs (%)[b] (Total No. = 214)	MAOIs/RIMAs (%)[c] (Total No. = 206)	Atypicals (%)[d] (Total No. = 85)
Dry mouth**	75.7	42.1	58.3	47.1
Constipation**	27.5	13.6	17.0	32.9
Dizziness	18.9	18.7	19.9	20.0
Drowsiness**	15.0	12.1	5.3	10.6
Headaches**	8.1	15.4	7.4	15.3
Tremors*	20.0	13.6	14.6	11.8
Anxiety**	1.6	10.3	1.9	7.1
Nausea**	4.4	12.1	3.4	8.2
Nocturnal urinary frequency*	14.0	7.9	11.2	5.9
Excessive sweating**	7.8	11.2	2.4	3.5

[a]61.5% of TCA users who reported adverse events received augmentation with lithium.
[b]16.4% of SSRI users who reported adverse events received augmentation with lithium.
[c]37.4% of MAOI/RIMA users who reported adverse events received augmentation with lithium.
[d]17.5% of users of atypical antidepressants who reported adverse events received augmentation with lithium.
*p < .05. **p < .001.

DISCUSSION

This study examined the effectiveness of antidepressants in a group of elderly depressed outpatients by investigating adverse events and depression prevalence over time. The drug utilization pattern in this study differs from those reported in other studies. Results indicate that tricyclic antidepressants were still commonly prescribed in our patient group but that there was an increase in the prescribing of SSRIs during the study period. Amitriptyline was shown to be a commonly prescribed antidepressant in the elderly, despite the fact that it has been deemed inappropriate for the aged population.[10,11] Doxepin was the most frequently prescribed antidepressant. The rationale for the high number of doxepin prescriptions includes the time frame of the analysis and the presence of cardiovascular comorbidities. SSRIs, with their reported safe cardiovascular profile, had just begun being marketed during the study period. Moreover, many patients required an antidepressant with a safe cardiovascular profile[12] before the advent of SSRIs. It may have been used preferentially in this particular clinic at that time given the fact that 36.7% and 26.1% of study patients had comorbid vascular and cardiac illnesses, respectively. No new prescriptions for doxepin were being made. Nortriptyline, also commonly used in our study, is reported to have a low anticholinergic profile and is associated with fewer cardiovascular and orthostatic hypotension events than the tertiary amines and as such appears to be more appropriate for the elderly.[13] When new prescriptions for tricyclics were written in this sample, nortriptyline was preferentially prescribed. SSRI utilization is increasing in the elderly.[11,14] This trend was reflected in our study by the high percentage of new prescriptions being written for SSRIs. It was also during this time that sertraline, fluvoxamine, and paroxetine became available for use in Canada. In the present study, sertraline was the most commonly prescribed SSRI. Sertraline may have been prescribed preferentially over fluoxetine because of its relatively short half-life. In this population, lithium was used as an augmentation agent. Evidence of lithium augmentation effectiveness in the elderly has come from small observational studies and case reports.[15,16]

Longitudinal results indicate that the MADRS score for a majority of study patients declined to below 18 after 2 months of antidepressant treatment. There was a significant difference between the 4 antidepressant classes, with

patients prescribed TCAs and MAOIs/RIMAs having shorter times to decline below the cutoff. During the next 6 months, more than a third of the patients did not reach a MADRS score of 18; however, no antidepressant class was shown to be superior. Finally, MADRS scores did not decline to below 18 during stage 3 (6 months and 2 years) for 37.1% of patients. Patients who were prescribed TCAs and MAOIs/RIMAs had longer durations below the cutoff during this stage. When the MADRS cutoff for depressive symptoms was lowered (secondary analysis) to include patients with mild and moderate-to-severe depressive symptoms, the time to decline below cutoff during stage 1 was longer and the time to increase to above the cutoff during stages 2 and 3 was shorter; however, only stage 3 showed a significant difference between the 4 drug classes, with patients prescribed TCAs and MAOIs/RIMAs having longer periods of wellness. These results may indicate a clinical advantage for prescribing TCAs and MAOIs/RIMAs in this group of elderly depressed patients since in our study they appeared to show better response with drugs from those classes for longer periods of time.

The most frequently reported adverse events for all drug classes were the anticholinergic symptoms, characterized by dry mouth, dry throat, and constipation. Other commonly reported adverse events (e.g., sedation, dizziness) may have been related to antihistaminergic and noradrenergic receptor affinities. Few cardiac effects were reported by study patients. Patients prescribed SSRIs also reported anticholinergic events along with the usually reported gastrointestinal (e.g., nausea, diarrhea) and central nervous system (e.g., insomnia, headaches) effects. Indeed, some of the most commonly reported events for study patients prescribed SSRIs were dry mouth and constipation.

Clinical recommendations for antidepressant dosing for elderly individuals has typically been one half to one third of the adult daily dose.[17] Examination of the doses in our study shows that the mean doses at the initial study visit for the different antidepressants were typically less than the recommended adult dose. Other observational studies have also recorded doses less than the recommended adult dose.[18] However, evidence is lacking supporting either the effectiveness or ineffectiveness of low-dose antidepressant treatment in the elderly. In contrast, randomized controlled trials conducted in elderly subjects have typically not adjusted doses for age. Some studies have utilized doses at the high end of the recommended adult dose.[3,19,20] Consequently, doses being utilized in elderly depressed patients in actual clinical settings may be different from those used in the "ideal world" of the randomized controlled trial. These differences may lead to alterations in response and tolerability rates.

Advantages of our observational study design include the collection of data from an actual clinical setting and the use of survival analysis. Survival analysis allows one to account and adjust for events of interest over time. This statistical technique was able to account for the differential visit rates of actual clinical patients. The study design enabled the collection of data unavailable from controlled trials. Preapproval and experimental studies are conducted over short durations and in controlled settings and thus do not examine how well antidepressants work in actual clinical environments. Our study was able to collect effectiveness information over the long term in that it permitted prospective longitudinal follow-up of a group of elderly outpatients. This should complement published experimental trial information.

The prevalence of depressive symptoms over time in our study may be due in part to the use of a cutoff score where patients were classified as either above or below a threshold value. The response rate in randomized controlled trials is defined differently (change from baseline or ≥ 50% decrease in depression score), and it is possible that many patients in this study classified as not depressed could still have had mild depressive symptoms. It is important to note that the durations of treatment were arbitrarily assigned. Stage 1 was meant to reflect acute treatment, and therefore 0 to 2 months was chosen. Most clinicians define the term *relapse* as the emergence of depressive symptoms within the first 6 months of treatment. Stage 2, 2 to 6 months, was intended to reflect the continuation phase. Recurrence occurs after relapse. Stage 3, 6 months to 2 years, was intended to reflect the maintenance phase. A continuous survival analysis could not be conducted over all treatment periods because of study inclusion criteria, which allowed individuals at any stage of therapy to be enrolled; as such, not all study individuals were assessed in every treatment stage. The ideal follow-up study would examine patients from stage 1 to stage 3 treatment periods. Despite the theoretical advantage of a complete longitudinal analysis, medication switches, lack of tolerability, and loss to follow-up would make such an analysis difficult.

Very few studies have examined the effectiveness of antidepressants in a prospective manner. Kamath and colleagues[21] examined the medical records of depressed outpatients at least 70 years of age. The retrospective review collected information on antidepressant outcomes such as improvement, recovery and discontinuation rates, and adverse events. That effectiveness analysis was based on the first antidepressant (i.e., SSRIs, secondary tricyclic amines, trazodone, or bupropion) prescribed for depression at one point in time. Determination of adverse events and treatment outcomes were based on progress notes in the medical records. Overall, 61% of patients discontinued antidepressant use and 26% improved or recovered. That study reported that patients had better outcomes if they were taking antidepressants for more than 3 months. Investigators reported taking differences in outcomes or adverse events between SSRIs and TCAs. There is no

mention of outcomes for atypical antidepressants. Limitations of that study include the fact that it was conducted in a retrospective manner using medical records and therefore subject to the biases of retrospective analyses and chart reviews. Moreover, effectiveness outcomes were not assessed with objective instruments. The present study was conducted in a prospective manner and examined outcomes of 4 antidepressant classes over time. Antidepressant outcomes were assessed with objective measures and TCAs were found to be more effective acutely and over the long term. A recent meta-analysis[1] reported no differences in terms of outcomes between any of the antidepressant classes (single-arm study) with the exception that TCA users had a significantly better outcome than SSRI users (comparative-arm study). However, those results are limited to acute randomized trials published in the literature.

In our study, subjects in all drug treatment groups reported high rates of anticholinergic-type symptoms. This was unexpected, since SSRIs are purported to have minimal anticholinergic, antihistaminergic, and cardiovascular adverse events and are thus considered to be the drug of choice in the elderly.[22] One study, however, reported that salivary flow rate was found to be decreased in patients prescribed both TCAs and SSRIs.[23] It is possible that the elderly population itself may be more vulnerable to these anticholinergic events because of comorbid illnesses and concomitant medications. The lack of cardiac adverse events in our study may be due to the fact that those events are more difficult to detect by the patient as opposed to the more bothersome events such as dry mouth and constipation. Systematic electrocardiograms or other cardiac evaluations were not conducted in these patients but may be necessary in future studies.

Our study had a number of methodological limitations including selection bias, type I and type II error, missing measurements, questionable interrater reliability, variable patient visits, pooling of results by antidepressant class rather than by drug, observational study design, and the potential lack of generalizability. *Selection bias* is defined as the bias inherent in the different ways patients are enrolled in a given study. The impact of selection bias in our study may not be great, because the entire sample consisted of an ambulatory sample rather than a mix of hospitalized and community samples. Moreover, all patients, rather than selected patients, who met eligibility criteria were recruited for the trial. Another type of selection bias is confounding by indication. The severity of the illness may lead to preferential treatment prescriptions. Treatment choice, and thus analysis, can be biased by the severity of the disease, comorbid illness, and concomitant medication. In this study, some patient assessments were not complete. Consenting patients could refuse to participate at any time in the study. Patient visits were variable in that patients came to the clinic from once a year to once a week. Scheduling separate visits for the study would eliminate the actual clinical component of practice-based research. This limitation is inherent to all practice-based observational studies, where the goal is to approximate usual clinical experience, not to control patients as in a rigid experimental trial. Methodological limitations should not prevent the development and execution of observational and pharmacoepidemiologic studies, as these studies provide the only glimpse of effectiveness in usual care situations.

CONCLUSION

This is the first study to systematically examine antidepressant effectiveness in a prospective observational design. In general, TCAs and MAOIs/RIMAs were shown to be superior in effectiveness during the 3 stages of treatment. Patients in the 4 antidepressant treatment groups reported similar adverse event profiles despite the variable receptor affinities. It is important to note that the results of this observational study are generalizable to a narrow population, namely elderly depressed outpatients receiving treatment in an academic, university-based hospital setting. More studies examining the effectiveness of pharmacotherapy in this population are needed.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil).

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