

## **COST-EFFECTIVENESS OF THE NEWER GENERATION OF ANTIDEPRESSANTS**

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In the last decade or so, several new antidepressants have been introduced into practice, including the selective serotonin reuptake inhibitors fluoxetine (1987), sertraline (1991), paroxetine (1992), and citalopram (1998), in addition to bupropion (1985), venlafaxine (1993), nefazodone (1994), and mirtazapine (1996). Two of these medications are available in delayed-release formulations: bupropion SR (1996) and venlafaxine XR (1997). Only one of these medications is currently available in a generic formulation (bupropion, 1999).

Each of these medications is more expensive in terms of acquisition costs than the older generation of tricyclics and heterocyclics and monoamine oxidase inhibitors. Together, the newer generations of antidepressants accounted for approximately \$7.7 billion in retail sales in the United States in 1999 (1), and antidepressants are second only to antibiotics in prescription sales by drug category.

Prices are of course subject to variation, but Table 78.1 shows that the "average wholesale price" for most of these medications is more than \$2 per day, according to the 2000 Drug Topics "Red Book" (2). Actual costs to health care systems or patients can be substantially lower or higher than the figures in Table 78.1 would indicate, depending on a number of factors. Certain health care systems are able to qualify for discounted prices for certain medications, and patients can sometimes receive medications free of charge via physician samples or indigent care programs. Acquisition costs are also lowered by patient noncompliance. In addition, some of the newer antidepressants are available as scored tablets (Table 78.1), so that patients taking lower doses have the opportunity to reduce costs substantially with only the modest inconvenience entailed by breaking the pills. However, higher doses of some medications lead to

higher acquisition costs when more than one pill is required for a particular dose. Regardless of these caveats, it is clear that the newer generation of antidepressants is more expensive to purchase than are the older generations.

Given their higher acquisition costs, it is important to determine whether these new, more expensive medications are cost-effective as first-line treatment in comparison with the older, less expensive antidepressants. In other words, in lay terms, are the newer medications worth the prices charged? Despite their higher acquisition costs, the newer antidepressants could be more cost-effective if they resulted in greater increases in quality of life and functioning, or in a reduction of the nonmedication costs of illness in comparison with the older antidepressants sufficient to offset their higher acquisition costs.

The impairments in quality of life and functioning and the nonmedication treatment costs associated with depression are large, and any improvements in these areas achieved with the newer antidepressants would clearly offset their higher purchase price. The World Health Organization has calculated that depression was the fourth leading cause of disease burden throughout the world in 1990, and projected that it would be the second leading cause by 2020 (3). The costs of depression to society as a result of productivity lost because of morbidity and mortality have been estimated at \$14.2 billion (in 1980) (4) and \$31.3 billion (in 1990) (5) in the United States. Moreover, direct treatment costs for depression, exclusive of medication acquisition costs, have been estimated at \$2.0 billion (in 1980) (4) and \$11.2 billion (in 1990) (5) in the United States. Most of these costs were related to hospitalization. The better tolerability of the newer versus the older antidepressants might well lead to reductions in these expensive treatment services.

A formal determination of whether the higher acquisition price of the newer antidepressants relative to the older antidepressants is offset by savings in other areas or increased benefits is traditionally conducted with a cost-effectiveness

**TABLE 78.1. AVERAGE WHOLESALE PRICE FOR A 30-DAY SUPPLY OF NEWER ANTIDEPRESSANTS**

Antidepressant	Strength (mg)	Dosing	Average Wholesale Price (\$)ª	
			Brand	Generic
Fluoxetine	10 <sup>b</sup>	QD	76.60	NA
	20		73.14	
	40		158.45	
Sertraline	25 <sup>b</sup>	QD	65.99	NA
	50 <sup>b</sup>		66.50	
	100 <sup>b</sup>		67.73	
Paroxetine	10	QD	66.95	NA
	20 <sup>b</sup>		56.97	
	30		71.95	
	40		76.00	
Citalopram	20 <sup>b</sup>	QD	60.51	NA
	40 <sup>b</sup>		63.14	
Bupropion	75	TID	65.97	64.87
	100		74.30	86.54
Bupropion SR	100	BID	85.51	NA
	150		91.64	
Venlafaxine	25 <sup>b</sup>	BID/TID	70.00/104.99	NA
	37.5 <sup>b</sup>		69.72/104.58	
	50 <sup>b</sup>		74.24/111.36	
	75 <sup>b</sup>		78.71/118.07	
	100 <sup>b</sup>		83.43/125.14	
Venlafaxine XR	37.5	QD	62.18	NA
	75		69.65	
	150		75.86	
Nefazodone	50	BID	74.11	NA
	100 <sup>b</sup>		74.00	
	150 <sup>b</sup>		74.00	
	200		74.11	
	250		74.00	
Mirtazapine	15 <sup>b</sup>	QD	69.72	NA
	30 <sup>b</sup>		71.83	
	45		76.50	

BID, twice daily; NA, not applicable; QD, daily; TID, three times daily.

ªLeast expensive price across suppliers, including repackaging houses. For QD dosing, the lowest cost for 30 pills was used, and 60 pills for BID dosing and 90 pills for TID dosing. When few or no suppliers offered lots of 30, 60, or 90 pills, the lowest-price 100-pill lot was multiplied by 0.3, 0.6, or 0.9, respectively, or the lowest-price 30-pill lot was multiplied by 2 or 3, respectively, whichever was lower. Unit dosing price excluded.

<sup>b</sup>Scored.

analysis. Cost-effectiveness is represented as a ratio between direct costs, the numerator, and changes in health status, the denominator. The relative cost-effectiveness of newer versus older antidepressants is represented as the incremental or marginal difference between the cost-effectiveness ratios determined for the newer and older antidepressants.

A cost-effectiveness model depends on many parameters, such as the effectiveness of alternative initial treatments, effectiveness of switching to secondary treatments, postulated lengths of treatment, and costs and health effects included.

The following are the major potential categories of costs and health effects (6). Direct costs are the resources con-

sumed in providing the intervention, in this case the treatment of depression, which includes dealing with side effects and other consequences. Direct costs are further subdivided into four major categories. The first category encompasses changes in the use of health care resources (e.g., the costs of medication acquisition, physicians and other personnel, laboratory and other services, and the appropriately apportioned capital costs of buildings and equipment). The second category of direct costs encompasses changes in the use of other resources (e.g., transportation costs). The final two categories encompass changes in the use of informal caregiver time and in the use of patient time for treatment.

Health effects are divided into two major categories. In

the first category, the intrinsic value of changes in health status, a value is placed on achieving or avoiding a specific health state. The health state may be characterized by using a single domain or multiple domains (e.g., changes in clinical status, functioning, and quality of life). The outcomes measured in any one of these domains can be intermediate (e.g., changes in the Hamilton Depression Scale) or distant (e.g., years of life gained). In practice, when intermediate outcomes are used, the health state and cost-effectiveness ratio is sometimes denoted simply in the native units of a single domain (e.g., cost per patient remitted from depression), and value weights are not assigned. In fuller analyses, weights are assigned to the benefits, and the weights are denominated in more comprehensive generic units that can be compared and combined across domains. The most common generic unit is the quality-adjusted life year (QALY).

The second category major category of health effects, indirect costs or productivity effects, refers to resource consumption attributable to changes in productivity caused by changes in morbidity or mortality.

In the most comprehensive cost-effectiveness analysis, these cost and health effects categories are applied to all sectors of health care, even if the specific intervention falls within a limited sector (e.g., treatment of depression within the mental health specialty sector). In more limited analyses, the categories are applied only in the specialty sector.

We should note that *costs* are not the same thing as *prices*. From an economic perspective, the term *costs* refers to the value of the resources consumed in providing/producing a service such as treatment of depression, most ideally calculated in terms of the consumed resources next-best use. The many types of *prices* that can be assigned to resources, and which are used in most studies, may or may not reflect the economic value of the resources consumed.

The conclusions suggested by any given cost-effectiveness analysis depend heavily on each of the factors we have listed: overall structure of the model, cost categories and specific cost values used, health effects categories, method of measuring health effects, and weights assigned to outcomes. The conclusions of the analysis also depend on its perspective—that is, for whom is the treatment cost-effective? The perspective determines which costs, benefits, and outcomes are potentially relevant and what weights are appropriate. Clarity about perspective is critical because in most contexts, various combinations of cost and benefits are borne by or accrue to different entities. For example, in a highly simplified and hypothetical case, if an HMO pays for prescriptions completely, and if the choice of a particular antidepressant results in higher total expenditures for drug purchase but allows patients to be less dependent on family members, the cost is borne by the HMO but the benefit is gained by the patient's family. In this case, the antidepressant might be cost-effective from the perspective of the patient's family or even from the broader perspective of society, but not from the perspective of the HMO.

Some of the perspectives commonly discussed or used include the following: patient or patient/family, employer/payer, individual health care institution (e.g., an HMO), national health care specialty sector (e.g., specialty mental health), national health care comprehensive system (i.e., including all health care sectors), and global societal (i.e., including *all* costs and *all* health effects) perspectives.

In considering whether the available studies suggest that newer antidepressants are cost-effective, we will limit ourselves to addressing the question from the two perspectives most commonly used in studies. First, we ask, "Are newer antidepressants cost-effective as first-line treatment from a health care system perspective?" In addressing this question with evidence from the available studies, one must appreciate that the studies to be reviewed have utilized multiple conceptualizations of cost-effectiveness. Some studies implicitly or explicitly assume equal effectiveness of newer and older antidepressants and ask whether the first-line use of newer antidepressants produces savings to the health care system in the direct treatment, nonmedication costs of treating depression that are sufficient to offset total direct treatment costs. Others model or measure clinical benefit and calculate average or incremental cost-effectiveness ratios. We report the authors' conclusions and discuss the limitations in design and methods. Most of the evidence regarding this first question is based on the perspective of a national health care comprehensive system, not merely of a mental health sector; consequently, the health care system perspective we address refers to all of health care, not just mental health care.

Second, we ask, "Are newer antidepressants cost-effective as first-line treatment from a global societal perspective?" Again, we review studies that utilize multiple conceptualizations of cost-effectiveness from this general perspective.

We also examine studies reporting relative rates of cost-effectiveness of the newer antidepressants.

To address our two major questions, we reviewed the recently published (July 1, 1995 to June 30, 2000) literature in English on antidepressants and cost analysis, focusing particularly on the newer antidepressants and updating our previous review (7). Relevant publications were identified by a search of Medline, Current Contents, and HealthSTAR computer databases and by manual bibliographic review. Studies available only as abstracts were not included. Other reviews of this topic have also been published recently (8–14).

The evidence most centrally relevant to the cost-effectiveness of antidepressants comes from studies that can be grouped into four methodologies: efficacy study metaanalyses, cost-effectiveness simulations, retrospective analysis of administrative databases, and prospective cost-effectiveness experiments. We review the data from each of these in turn. We also review briefly the data on whether a decrease in deaths from suicide is a benefit that favors the newer antidepressants.

## EFFICACY AND TOLERABILITY METAANALYSES

Efficacy and tolerability studies provide information on expected percentages of responders and dropouts, which are central parameters in cost-effectiveness calculations, in addition to information on side effect burden. Cost-effectiveness simulations (see next section) often use data from efficacy metaanalyses.

Numerous metaanalyses of randomized short-term trials of selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs) are now available (Table 78.2), as are several metaanalyses of trials comparing non-SSRI newer antidepressants with older, control antidepressants (Table 78.3). These metaanalyses include several monumental efforts with careful attention to the unbiased inclusion of studies and minimization of publication bias. To simplify the presentation, Table 78.2 shows the original

authors' conclusions about the identified principal efficacy and tolerability measures. These authors often considered treatment continuation as an efficacy measure, and treatment discontinuation for side effects as a tolerability measure. A metaanalysis of placebo-controlled comparisons in 49 studies from 1966 through 1995 that included an investigational antidepressant and a reference antidepressant (15) and two other metaanalyses (16,17) are not included in Table 78.2 because it is not clear whether the reported effect sizes for TCAs and SSRIs are restricted to the trials internally comparing TCAs with SSRIs. The results of the metaanalyses in Table 78.2 are remarkably consistent. Perhaps the consistency is not surprising given that the articles report on highly overlapping sets of clinical trials. The metaanalyses almost uniformly conclude that these two classes of antidepressant are quite similar in regard to efficacy. Only one analysis found evidence of greater efficacy for the SSRIs in comparison with a subgroup of older TCAs; another found

**TABLE 78.2. METAANALYSES OF STUDIES COMPARING SSRIs WITH OLDER CONTROL ANTIDEPRESSANTS FOR MAJOR DEPRESSION**

Reference	Newer AD	Control AD	Inclusion Criteria	No. Studies <sup>a</sup>	Reported Advantage	
					Efficacy	Tolerability
Song et al., 1993 (18)	SSRIs	TCAs and related ADs	Double-blinded published	58	NC	N>C
Montgomery et al., 1994 (19)	SSRIs	TCAs	Double-blinded published	42	—	N>C
Anderson and Torrenson, 1995 (20)	SSRIs	TCAs	Double-blinded published	62	NC	N>C
Hotopf et al., 1997 (65)	SSRIs	Older TCAs Newer TCAs Heterocyclic ADs	Randomized published	51 24 17	N>C NC NC	—
Steffens et al., 1997 (66)	SSRIs	TCAs	Double-blinded published	36	NC	N>C
Anderson, 1998 (67)	SSRIs	TCAs and related ADs	Double-blinded inpatient	25, 23	C>N	N>C
Trindade et al., 1998 (68)	SSRIs	TCAs	Double-blinded	84	—	NC <sup>b</sup>
Mulrow et al., 1998 (69)	SSRIs	TCAs	Randomized	43, 76	NC	N>C
Bech et al., 2000 (70)	Fluoxetine	TCAs	Randomized	25	NC	N>C
Geddes et al., 2000 (71)	SSRIs	TCAs	Double-blinded	71	NC	—
Anderson, 2000 (72)	SSRIs	TCAs	Randomized published	102, 95	NC	N>C
Williams et al., 2000 (73)	SSRIs	Older TCAs Newer TCAs Tetracyclics	Randomized	38 5 7	NC NC NC	N>C N>C NC

AD, antidepressant; C, control; N, newer; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

<sup>a</sup>When two numbers are shown, the first is the number of studies in the efficacy analysis and the second the number in the tolerability analysis.

<sup>b</sup>Significant for adult outpatient studies but not for the entire group.

**TABLE 78.3. METAANALYSES OF STUDIES COMPARING NON-SSRI NEWER ANTIDEPRESSANTS WITH OLDER CONTROL ANTIDEPRESSANTS FOR MAJOR DEPRESSION**

Reference	Newer AD	Control AD	Inclusion Criteria	No. Studies <sup>a</sup>	Reported Advantage	
					Efficacy	Tolerability
Stahl et al., 1997 (74)	Mirtazapine	Amitriptyline	Sufficiently similar	4	NC	N>C
Srisurapanont, 1998 (75)	Nefazodone Mirtazapine Venlafaxine	TCA nTCA SSRI	Randomized	17, 13	N>C	NC <sup>b</sup>
Mulrow et al., 1998 (69)	SNRIs <sup>c</sup>	TCA	Randomized	8, 9	NC	N>C
Williams et al., 2000 (73)	SNRIs <sup>d</sup> 5-HT <sub>2</sub> antagonists	Older TCA Older TCA	Randomized	6 5	NC NC	NC —

5-HT, serotonin; AD, antidepressant; C, control; N, nerve; nTCA, nontricyclic antidepressant; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

<sup>a</sup>When two numbers are shown, the first is the number of studies in the efficacy analysis and the second the number in the tolerability analysis.

<sup>b</sup>N>C for comparisons vs. TCAs, NC for comparisons vs. nTCAs and SSRIs.

<sup>c</sup>Includes venlafaxine and mirtazapine.

<sup>d</sup>Includes venlafaxine, mirtazapine, and milnacipran.

evidence for greater efficacy of TCAs when attention was restricted to inpatients, and the other eight metaanalyses reported similar efficacy for TCAs and SSRIs.

The metaanalyses also conclude almost uniformly that the SSRIs have a small but consistent tolerability advantage over the TCAs in these short-term randomized trials. Nine of ten studies investigating tolerability found evidence of greater tolerability for the newer agents, but in general, the magnitude of the effect was relatively small. For example, dropout rates attributed to side effects were 15.4% versus 18.8% (18), 14.9% versus 19.0% (19), and 14.4% versus 18.8% (20) for SSRIs versus TCAs in three of the early metaanalyses.

The small size of the SSRI acceptability advantage in the efficacy studies is surprising, given the widespread entry of the SSRIs into clinical practice. Studies of antidepressant use in naturalistic practice often find a more pronounced tolerability advantage (21–26). Alternative explanations for this discrepancy are possible. Studies suggest that patients who enroll in randomized trials may differ from the general clinical population (27,28), and it is possible that patients who enroll in clinical trials are more tolerant of side effects than average. On the other hand, because these naturalistic studies are not double-blinded, patients in clinical practice could be influenced by expectancy effects.

## COST-EFFECTIVENESS SIMULATIONS

Cost-effectiveness simulations most commonly construct mathematical models of clinical practice based on decision analysis. Usually, pathways of branching alternative treat-

ment options and outcomes are created. Costs, probabilities, and in some cases value weights or utilities for outcomes are assigned to the alternatives. Typically, the values for these parameters are derived from metaanalyses, literature reviews, administrative databases, or expert panels. In addition to medication acquisition costs, these models can include any subset of the costs we defined above.

A substantial number of simulations have been published. Table 78.4 shows data from 19 published simulations comparing SSRIs with older control antidepressants. Table 78.5 shows data from nine simulations comparing newer non-SSRI antidepressants with controls. For each study, Tables 78.4 and 78.5 show the medications compared, duration of the simulation, authors' apparent principal cost-effectiveness outcomes, authors' conclusions about relative cost-effectiveness, and a brief summary of methodologic limitations. Two additional mirtazapine simulations from U.K. and Swedish health care system perspectives are described in a review (11). Results were similar to those of the French and Austrian simulations (Tables 78.4 and 78.5).

A simple "vote counting" across studies in Table 78.4 shows that most of the simulations concluded that SSRIs are more cost-effective than TCAs (10 favor SSRIs, six favor TCAs, and two are ties). Table 78.5 shows that eight of nine simulations favor the cost-effectiveness of newer non-SSRI antidepressants over older agents. Simple vote counting is problematic because it ignores numerous methodologic limitations of the individual studies. At least equally as problematic is the fact that the methodologic problems may far exceed those that are apparent; often, the published models are not "transparent," meaning that they fail to spec-

TABLE 78.4. COST-EFFECTIVENESS SIMULATION STUDIES COMPARING SSRIs WITH OLDER CONTROL ANTIDEPRESSANTS

Study (Reference)	Newer AD(s), Population	Control AD(s)	Treatment Length <sup>a</sup>	Principal Outcome	Analysis Favors <sup>b</sup> detail	Methodologic Limitations
Boyer and Feighner, 1993 (76)	fluoxetine, sertraline, first episode	amitriptyline, imipramine, nortriptyline, desipramine, imipramine	6 mo	direct cost per pt	Newer	1. model not fully transparent 2. short treatment durations 3. initial success rates overly different
Jonsson 1993 (34) Jonsson and Bobbington, 1994 (35) Stewart, 1994 (38)	paroxetine, U.K. primary care	imipramine	a-12 wk m-12 wk	direct cost per tx success	Newer	1. no success for switch tx 2. short treatment durations 3. initial success rates overly different 4. equal tx delivery costs
McFarland, 1994 (37)	sertraline, paroxetine, primary care paroxetine, primary care	amitriptyline, imipramine, imipramine	a-12 wk m-26 wk 1:6 mo 2:12 mo	direct cost per tx success primary care cost per pt	i>a>p>s Control 1:ip 2:i>p Control Newer	1. tx failure costs possibly somewhat low 2. equal tx delivery costs 1. limited perspective 2. initial success rates
Hatziaandreu et al., 1994 (77)	sertraline, young female recurrent	dothiepin	a-3 mo m-2 Y+	lifetime direct costs per saved discounted QALY	Newer	1. maintenance vs. episodic tx confounded across drug
Lapierre et al., 1995 (31) Anton and Revicki, 1995 (78)	paroxetine, Canada primary care fluoxetine, young female recurrent, Canada	imipramine, imipramine	a-6 mo m-4 mo 9 mo <sup>c</sup>	direct cost per pt discounted direct cost per QALY	Newer Newer	1. no dc of switch tx when failure 2-4. similar to (34,35) 1. multiple unreported probabilities 2. health state utility generation methods not described
Revicki et al., 1995 (79)	fluoxetine, young female recurrent, U.S.	imipramine	9 mo <sup>d</sup>	discounted direct cost per QALY	Newer	1. variability for utilities not reported

Nuijten et al., 1995 (80)	citalopram, unspecified	three TCAs	12 mo	direct cost per pt	Newer	1. similar to (77) 2. treatment duration unspecified
Einarsen et al., 1995 (81)	SSRIs inpt start	TCAs	300 d	direct cost per symptom-free day	H>T>S	1. high delivery costs for TCAs
Einarsen, et al., 1995 (81)	SSRIs, outpt start	TCAs	300 d	direct cost per symptom-free day	H>S>T	2. initial success rates overly different
Hylan et al., 1996 (32)	fluoxetine, primary care	HCA <sup>s</sup> imipramine	6 mo	direct plus indirect cost per cured pt	Control	1. high delivery costs for TCAs 2. initial success rates overly different 1-3. similar to (34,35)
Bentkover and Feighner, 1996 (30)	paroxetine, primary care and psychiatry	imipramine	a-6 mo m-none	direct cost per pt	Newer	1-4. similar to (31)
Woods and Rizzo, 1997 (82)	paroxetine, primary care	imipramine	a-34 wk m-78 wk	direct cost per tx success	Control	1. improved version of (34,35)
Einarsen et al., 1997 (83)	SSRIs, Ontario inpt start	TCAs	6 mo	direct cost per tx success	Tie	1. metaanalysis comparisons indirect 2. short tx duration
Einarsen et al., 1997 (83)	SSRIs, Ontario outpt start	TCAs	6 mo	direct cost per tx success	Newer	1. metaanalysis comparisons indirect 2. short tx duration
Canadian Office, 1998 (84)	SSRIs, Canada, site unspecified	TCAs alone TCAs/switch	a-3 mo m-6 mo	various direct cost ratios	Control	1. report brief
Brown, et al., 1999 (85)	fluoxetine, Austria, moderate severe	amitriptyline	~6 mo	direct cost per pt and tx success, lost productivity	Tie	1. mirtazapine vs. fluoxetine based on one study 2. reliance on Delphic panel 3. hospitalization estimates high

<sup>a</sup>Duration of specific treatment phases is shown if available. If not specified, the overall simulation length is shown. a, duration of successful acute plus continuation treatment; wk, weeks; m, duration of successful maintenance treatment; tx, treatment; dc, discontinuation; mo, months; pt, patient.

<sup>b</sup>Authors' conclusions. AD, antidepressant(s); T, TCA; S, SSRI; C, Control AD(s).

<sup>c</sup>Nine months for first recurrence, then lifetime if second recurrence.

<sup>d</sup>Nine months for first recurrence, then 27 months if second recurrence.

<sup>e</sup>Heterocyclic antidepressants maprotiline and trazodone.

QALY, quality-adjusted life year; >, more cost-effective

TABLE 78.5. COST-EFFECTIVENESS SIMULATION STUDIES COMPARING NEWER NON-SSRI WITH CONTROL ANTIDEPRESSANTS

Study (Reference)	Newer AD(s), Population	Control AD(s)	Treatment Lengths <sup>a</sup>	Principal Outcome	Analysis Favors <sup>b</sup> detail	Methodologic Limitations
Anton and Revicki, 1995 (78)	nefazodone, young female recurrent, Canada	imipramine fluoxetine	9 mo <sup>c</sup>	discounted direct cost per QALY	n>f>i Newer	1. multiple unreported probabilities 2. health state utility generation methods not described
Revicki et al., 1995 (79)	nefazodone, young female recurrent, U.S.	imipramine fluoxetine	9 mo <sup>d</sup>	discounted direct cost per QALY	n>f>i Newer	1. variability for utilities not reported
Einarsen et al., 1995 (81)	venlafaxine, input start	TCAs HCA <sup>s</sup> <sup>e</sup> SSRIs	300 d	direct cost per symptom-free day	v>H>T>S Newer	1. high delivery costs for TCAs 2. initial success rates overly different
Einarsen et al., 1995 (81)	venlafaxine, output start	TCAs HCA <sup>s</sup> <sup>e</sup> SSRIs	300 d	direct cost per symptom-free day	H>v>S>T Control	1. high delivery costs for TCAs 2. initial success rates overly different
Montgomery et al., 1996 (33)	nefazodone, U.K. primary care	imipramine	a = 12 wk m = 12 wk	direct cost per tx success	Newer	1–4. similar to (34,35)
Einarsen et al., 1997 (83)	venlafaxine, Ontario input start	TCAs SSRIs	6 mo	direct cost per tx success	v>f,T Newer	1. metaanalysis somewhat indirect 2. short treatment duration
Einarsen et al., 1997 (83)	venlafaxine, Ontario output start	TCAs SSRIs	6 mo	direct cost per tx success	v,f>T Newer	1. metaanalysis somewhat indirect 2. short treatment duration
Brown et al., 1999 (86)	mirtazapine, France, moderate/severe	amitriptyline	28 wk	direct cost per tx success, lost productivity	Newer	1. reliance on Delphic panel 2. brief duration
Brown et al., 1999 (85)	mirtazapine, Austria, moderate/severe	amitriptyline fluoxetine	~6 mo	productivity direct cost per pt and tx success, lost productivity	m>a m>f Newer	1. mirtazapine vs. fluoxetine based on one study 2. reliance on Delphic panel 3. hospitalization estimates

Legend: see Table 78.4.

ify clearly the inputs to the model and exactly how the computations were made. This is critical because, as we noted above, the results of any simulation are dependent entirely on the many details of the model. When these details are not stated, it is not possible for the reader independently to look for errors in critical assumptions or independently to conduct “sensitivity analyses” of the values of input parameters to evaluate the resulting impact on the models’ conclusions.

Other concerns arise about the simulations as a consequence of their sensitivity analyses. Generally, these studies report that results are not sensitive to any of the variations that they show in inputs. This raises concerns because if a simulation is properly designed, and if it contains no calculation errors, it ought to be sensitive to at least extreme variations in some inputs. One approach is to show what input values would be required for the medications to “break even” (29). The reader can then come to an opinion about whether the break-even inputs are reasonable possibilities or not.

The input values required to reverse the cost-effectiveness conclusion may be unreasonably high or low, but demonstration that the model is sensitive to input variation increases confidence in the integrity of the model and in the reported lack of sensitivity to less extreme variations. For example, if it is not possible to demonstrate the cost-effectiveness of TCAs when the acquisition cost of SSRIs is increased 1,000-fold, something is wrong with the model. In many of the decision analytic simulations concluding that the newer antidepressants are more cost-effective (30–33), the design and assumptions were very similar to those in an early model of SSRIs versus TCAs (34,35). This simulation was reported very explicitly and so is transparent and could be replicated by others. When the model was replicated, a design flaw was discovered and unrealistic assumptions were identified that drove the results (29). Correction of the design flaw and substitution of longer treatment lengths recommended by practice guidelines reversed the findings and yielded a cost-effectiveness advantage in favor of the TCAs. These same corrections could be applied to the other simulations that depended on the early example. The Australian Pharmaceutical Benefits Scheme reported similar significant problems with 67% of the pharmacoeconomic simulations it received in support of efforts to meet regulatory requirements for registration of new drugs in that country (36).

This limitation of short time horizons for the simulations is relatively common in the studies shown in Tables 78.4 and 78.5. In general, the longer treatment with antidepressants is continued, the less cost-effective the newer antidepressants as first-line treatment are likely to be. A longer treatment period progressively increases the medication acquisition costs associated with newer antidepressants. By contrast, much of the greater cost of treatment delivery of the older drugs is expended early in treatment, in visits

for dose titration and management of side effects. Longer treatment periods progressively dilute this early cost over time. Of the only two simulations in which sensitivity analysis of treatment length was performed (29,37), both showed cost-effectiveness advantages for the inexpensive drug as length of treatment length increased, and one simulation utilizing intermediate treatment lengths favored the TCAs (38).

Given the subtle but powerful effect of the many details of cost-effectiveness simulations, many have expressed concern that these simulations may harbor critical biases that are difficult to expose. For example, one leading journal has taken the stance that cost-effectiveness simulations are more vulnerable to conflict of interest than other types of research, and it declines to publish any cost-effectiveness simulations (39).

In this regard, it may be noted that all the 15 simulations funded by industry shown in Tables 78.4 and 78.5 reported their own products to be more cost-effective than older control antidepressants. Of the studies sponsored by companies manufacturing newer non-SSRI antidepressants, four of six found the SSRIs to be less cost-effective than or tied with older antidepressants, and four of six found their own products to be more cost-effective than SSRIs. In both of the two studies funded by government, the SSRIs were less cost-effective than the TCAs when provisions were made for patients intolerant to TCAs to switch. The source of funding was not identified in three studies.

## RETROSPECTIVE ANALYSES OF ADMINISTRATIVE DATABASES

Retrospective administrative database studies are a source of data on antidepressant costs and efficacy in actual clinical practices. In these studies, computerized pharmacy and service utilization records are used to analyze cost outcomes as a function of clinical assignment to antidepressant. Retrospective studies are less expensive than prospective trials and can be conducted more quickly. However, they are much more vulnerable to questions about the interpretation of results for several reasons. These studies are vulnerable to “selection bias.” Patients are not randomly assigned to treatment; therefore, it is likely that the constructed groups may not be comparable in some important way at baseline. They are also vulnerable to “cohort effects.” The retrospective groups may be drawn from different time frames. Apparent differences between treatments may in fact be a consequence of changing trends in practice over time (40).

Database studies generally lack any direct measure of clinical outcome. As a result, they generally assume a worst case of equivalent outcomes for the newer antidepressants and the older antidepressants and then defined the more cost-effective care as the treatment associated with lower overall costs of health care. A newer antidepressant can be

**TABLE 78.6. RETROSPECTIVE COST-EFFECTIVENESS ANALYSES OF ADMINISTRATIVE DATABASES: SSRI<sub>s</sub> VERSUS OLDER ANTIDEPRESSANTS**

Reference, N, time frame	Population	Newer AD(s)	Control AD(s)	Principal Outcome	Analysis Favors <sup>b</sup> detail	Methodologic Limitations
Sciar et al., 1998 (42) N = 550 7/1/88–12/31/91	U.S. HMO single-episode depressed patients initiating AD	fluoxetine	amitriptyline nortriptyline	depression-related 12-mo health care expenditures	f>T Newer	1. determination of depression relatedness of concern 2. very high doses of n 3. no breakdown of high TCA costs 4. possible cohort effect 1–4. as for (42) 5. possible uncorrected selection bias
Sciar et al., 1994 (87) N = 701 1/1/89–10/31/93	U.S. HMO depressed pts who stayed on initial AD for 12-mo	fluoxetine	amitriptyline nortriptyline desipramine	as for (42)	f>T Newer	1–5. as for (87)
Skaer et al., 1995 (88) N = 823 1/1/89–6/30/94	U.S. HMO single-episode depressed pts who stayed on initial AD for 12-mo	sertraline	amitriptyline nortriptyline desipramine	as for (42)	s>T Newer	1–5. as for (87)
Forder et al., 1996 (89) N = 398 time frame not stated	U.K. general practice pts selected from a clinical trial and matched controls	sertraline	TCA <sub>s</sub>	direct and partial indirect 12-mo cost per successfully treated pt	s>T Newer	1. subsample selection not random 2. shorter treatment length for s (168 d) than T (278 d) reduces cost of s 3. selection bias <sup>a</sup> or cohort effect
Groghan et al., 1997 (41,90) N = 1,242 1990–1992	U.S. privately insured depressed patients treated in primary care	fluoxetine	4 TCA <sub>s</sub> trazodone	total medical charges for 12-mo	fC Tie	1. high cost of other drugs for trazodone 2. possible uncorrected selection bias 3. possible cohort effect 4. ?effects of previous treatment 5. ?no adjustment for baseline costs
Thompson et al., 1998 (91) N = 1,661 7/91–6/93	New England private insurer depressed patients	SSRI <sub>s</sub>	TCA <sub>s</sub>	nonpsychiatric health care costs for 12-mo	Tie	1. possible uncorrected selection bias 2. possible cohort effect 3. ?effects of previous treatment 4. no adjustment for baseline costs

Hylan et al., 1998 (92) N = 2,693 1990–1994	U.S. fee-for-service depressed patients, insured by 20 large employers	fluoxetine sertraline paroxetine	TCAs	total health care costs for 12-mo	f>T 1/3 Newer	1. possible uncorrected selection bias 2. possible cohort effect 3. ?effects of previous treatment 4. no adjustment for baseline costs
Crown et al., 1998 (93) N = 3,439 1990–1994	U.S. fee-for-service depressed patients, insured by large employers	fluoxetine sertraline paroxetine	TCAs	total health care costs for 12-mo	S>T Newer	1. possible uncorrected selection bias 2. possible cohort effect on costs 3. possible effect of previous treatment on costs 4. no adjustment for baseline costs
Croghan et al., 2000 (46) N = 2,557 1990–1994	U.S. fee-for-service depressed patients, insured by ~20 large employers	fluoxetine sertraline	TCAs	psychiatric hospitalization for 12-mo	f>T sT 1/2 Newer	1. possible uncorrected selection bias 2. possible cohort effect 3. possible effect of previous treatment
Simon 1998 (47) N = 5,169 1/1/92–6/30/94	U.S. HMO depressed patients	fluoxetine	imipramine desipramine	total health care costs for 6-mo	fT Tie	1. possible uncorrected selection bias 2. possible cohort effect
Smith 1996 (94) N = 152 1994	U.S. HMO, ICD-9 major depression, received AD 3 mo, excluded if switched drug	SSRIs	TCAs	as for (87)	Tie	1–2. as for (87) 3. possible selection bias
Sullivan 2000 (95,96) N = 981 1993–1997	9 U.S. health plans second-line treatment	SSRIs	TCAs	total health care costs for 12-mo	Tie	1. possible uncorrected selection bias 2. possible cohort effect
Sclar 1999 (43) N = 1,339 1/1/96–4/30/99	as for (42)	fluoxetine sertraline paroxetine citalopram	amitriptyline	depression-related 6-mo health care expenditures	f, p, C>S, a 3/4 Newer	1. N = 71 for citalopram 2. possible uncorrected selection bias 3. possible cohort effect

Legend: see Table 78.4.

associated with lower overall costs of health care if the higher acquisition costs are more than offset by lower costs for other services. This type of cost-effectiveness analysis is known as *cost minimization*.

A few of the administrative database studies have constructed proxy outcome measures based on pharmacy refill data, such as “number of prescriptions refilled” (41). For example, one study used pharmacy claims to determine the duration of antidepressant treatment and then held that longer care is likely to be more beneficial. This study found fluoxetine to be associated with longer continuation on medication and costs similar to those of the comparison groups. The authors concluded that fluoxetine is cost-effective because adherence to treatment guidelines is better with no increment in cost. Other retrospective analyses have reported similar natural course of therapy findings but base a judgment of cost-effectiveness on finding a reduction in overall “depression-related” health care costs (42,43).

We briefly review the designs and results of available retrospective administrative database studies in Tables 78.6, 78.7, and 78.8. Table 78.6 lists studies comparing SSRIs with older antidepressants. Table 78.7 lists studies making comparisons among SSRIs, and Table 78.8 presents one study comparing a newer non-SSRI with control antidepressants. These tables indicate for each study the sample size in the administrative database, the time interval over which data were sampled, the type of patient population, the newer and control antidepressants analyzed, the stated principal economic outcome measure, the overall results on that outcome measure as interpreted by the authors, and a brief discussion of methodologic limitations. One small pilot study is not included in Table 78.6 (44), and a published retrospective database study not included in Table 78.6 reportedly found fluoxetine to be cost-effective in comparison with TCAs (Skaer et al., 1996; cited in ref. 12).

Simple vote counting across the studies in Table 78.6 shows that the majority have concluded that SSRIs are more cost-effective than TCAs (seven favor at least one of the studied SSRIs, none favor TCAs, and five are ties). Again, simple vote counting is unsatisfactory because these studies are subject to numerous methodologic limitations.

The most important limitation of the studies in Table 78.6 is a possible cohort effect; the distribution of starts of different antidepressants may have changed during the study interval (40,45). During this time period, important influences on clinical practice totally unrelated to which antidepressant was used may have changed, so that the influence of starts on one type of antidepressant versus another may have been confounded with the effect of changes in clinical influences. For example, during the period encompassed by the first study in Table 78.6, fluoxetine progressively gained market share, while at the same time health care organizations independently reduced expenditures through tighter management. Thus, a higher proportion of TCA starts may have occurred early in the study period,

when care was not so firmly managed, and a higher proportion of fluoxetine starts may have occurred later in the study period, when visits and hospitalizations were more carefully scrutinized. Thus, cost savings in later years could erroneously be attributed to fluoxetine that are really a consequence of tighter management. The distribution of fluoxetine and TCA starts within the study period was not reported.

In relation to the problem of cohort effects, recent studies have included time of the antidepressant start within the study interval as an explanatory variable in the analysis, but they appear to have restricted attention primarily to its effect on initial selection of antidepressant. No study presents data indicating whether health care costs associated with antidepressant starts were increasing or decreasing during the study interval, or how a secular cost trend, if present, may have interacted with the distribution of starts of individual antidepressants during the study interval.

Other important limitations in the studies in Table 78.6 include a tendency not to adjust the analysis for baseline costs in some of them.

Table 78.7 shows the results of administrative database studies comparing cost-effectiveness among SSRIs. The first three studies, which sampled data from 1989 to 1994, found fluoxetine to be more cost-effective than sertraline or more cost-effective than sertraline and paroxetine. A type of selection bias that has been termed *launch bias* may have affected these findings (46). The time frames of these studies overlapped with the first year or two after launch of sertraline and paroxetine. It is possible that a new antidepressant is prescribed for a different type of patient in the early years after its launch than after it has been on the market for several years. Patients selected by their physicians to receive a brand-new antidepressant may generally be more severely ill than other patients. Recent analyses have attempted to control for initial severity. However, another possibility is that patients selected by their prescribers to receive a brand-new antidepressant may on average have been more resistant to previous treatment than other patients. Because treatment resistance correlates only partially with severity, adjustment for severity of illness may only partially correct a launch bias effect driven by treatment resistance. Most studies attempting to control for previous treatment eliminate patients who received antidepressants in the 4 to 6 months before the start of the index antidepressant. Although this exclusion is somewhat reassuring, it still does not prevent patients from being included in the analysis who were taking an antidepressant at the start of the study interval, then stopped antidepressant therapy for 4 to 6 months, perhaps because of ineffectiveness, then started a different, recently launched antidepressant identified as the index. Such patients would be predicted to be relatively unlikely to respond to treatment and relatively likely to incur treatment costs subsequent to the antidepressant start. To the extent that

**TABLE 78.7. RETROSPECTIVE COST-EFFECTIVENESS ANALYSES OF ADMINISTRATIVE DATABASES: COMPARISONS AMONG SSRIs**

Reference, N, time frame	Population	Newer AD(s)	Principal Outcome	Authors' Conclusions	Methodologic Limitations
Sclar et al., 1995 (97) N = 744 1/1/89–3/31/94	U.S. HMO single-episode depressed pts who stayed on initial AD and received at least 3 Rxs	fluoxetine sertraline paroxetine	as for (87)	f>s,p	1. possible uncorrected selection bias 2. possible cohort effect
Hylan et al., 1998 (92) N = 2,693 1990–1994	U.S. fee-for-service depressed patients, insured by 20 large employers	fluoxetine sertraline paroxetine	total health care costs for 12 mo	f>s	1. possible uncorrected selection bias 2. possible cohort effect 3. ?effects of previous treatment 4. no adjustment for baseline costs
Croghan et al., 2000 (46) N = 2,557 1990–1994	U.S. fee-for-service depressed patients, insured by ~20 large employers	fluoxetine sertraline	psychiatric hospitalization for 12 mo	f>s	1. possible uncorrected selection bias 2. possible cohort effect 3. possible effect of previous treatment
Russell et al., 1999 (98) N = 2,342 1995–1996	U.S. depressed patients contributing data to a publicly available claims database	fluoxetine sertraline paroxetine	total health care costs for 12 mo	f s p	1. possible uncorrected selection bias 2. possible effect of previous treatment
Sclar et al., 1999 (43) N = 1,339 1/1/96–4/30/99	as for (42)	fluoxetine sertraline paroxetine citalopram	depression-related 6 mo health care expenditures	f,p,<s	1. N = 71 for citalopram 2. possible uncorrected selection bias 3. possible cohort effect

Legend: see Table 78.4.

**TABLE 78.8. RETROSPECTIVE COST-EFFECTIVENESS ANALYSES OF ADMINISTRATIVE DATABASES: NON-SSRIs VERSUS CONTROL ANTIDEPRESSANTS**

Reference, N, time frame	Population	Newer AD(s)	Control AD(s)	Principal Outcome	Authors' Conclusions	Methodologic Limitations
Sullivan et al., 2000 (95,96) N = 981 1993–1997	9 U.S. health plans second-line treatment	venlafaxine other – nefazodone bupropion trazodone	TCAs SSRIs	total health care costs for 12 mo	v,o,S,T	1. possible uncorrected selection bias 2. possible cohort effect

Legend: see Table 78.4.

such patients are included in an analysis, a launch bias may exist that is unfavorable to the second antidepressant.

In the first study in Table 78.7, the sample was restricted to DSM-IV 296.2 “single-episode” depressed patients. This restriction was intended to reduce the possibility of a selection bias if the patients chosen to receive the newest medications were more refractory as a group than patients chosen to receive more established medications. This possibility may still have influenced the analysis because in subsequent studies, it was found that some patients with “single-episode” depression had had previous episodes that were treated with antidepressants (42,43).

The fourth study in Table 78.7 is consistent with a launch bias interpretation of the three earlier studies. In this study, the time horizon (1995 through 1996) was 3 to 4 years after the launch of sertraline and paroxetine. This study found the three SSRIs to be equally cost-effective. Limited retrospective data suggest that venlafaxine and other newer non-SSRI antidepressants are similar to SSRIs and TCAs in cost-effectiveness (Table 78.8).

The retrospective database method may be especially vulnerable to publication bias. Because the retrospective studies are inexpensive in comparison with prospective trials, and because the number of potential study sites is large, the possibility is greater with retrospective studies that multiple analyses are conducted but only a limited number published.

### PROSPECTIVE COST-EFFECTIVENESS TRIALS

Prospective randomized cost-effectiveness experiments offer a potential “gold standard” methodology for investigating cost-effectiveness because of the internal validity arising from the randomization. In addition, they directly collect data on both outcomes and costs. The randomization permits the investigator to ascribe any observed differences in cost-effectiveness among treatment groups to the treatment itself and not to unmeasured baseline differences among the groups. The major difficulty with prospective randomized

cost-effectiveness experiments, in addition to their expense and the time required to complete them, is the question of external validity. Are the patients who consent to random assignment representative of the entire group of patients in routine practice, or are they different in some important way? Relatively little attention has been paid to this issue in depression research, although in one study, the patients participating in a randomized trial of depression had significantly fewer comorbid diagnoses than did excluded patients and were more likely to have a single episode of depression (27).

At present, only two prospective pharmacoeconomic studies examining the cost-effectiveness of newer antidepressant treatment have been published. The initial report from the first study included data up to 6 months after randomization (4). Patients were followed for 2 years after randomization, and the long-term data were reported recently (26). Patients were enrolled from participating primary care clinics in a large HMO in the United States. Patient out-of-pocket copayment prescription expenses were waived. Patient identification depended on primary care physician referral. Physicians were asked to refer patients whom they were starting on an antidepressant for depression when both patient and physician were willing to consider random assignment. Of 621 patients referred, 579 (93%) were eligible, and 536 (93%) consented and were randomized. At baseline, 67% of randomized patients met DSM-III-R criteria for major depression; the remainder met criteria for either minor depression or dysthymia. The average score on the Hamilton Depression Scale at baseline was below 14. Patients were randomly assigned to receive fluoxetine ( $N = 173$ ) or the commonly prescribed TCAs imipramine ( $N = 182$ ) or desipramine ( $N = 181$ ). After randomization, the patients were free to switch antidepressants. Evaluators but not patients or prescribing physicians were blinded to the initial treatment assignment. Randomized patients were evaluated at baseline and at 1, 3, 6, 9, 12, 18, and 24 months with measures of symptoms, quality of life, and service utilization.

At the 6-month follow-up, the proportion of patients continuing on the original antidepressant was nearly 60%

for fluoxetine, less than 40% for imipramine, and approximately 30% for desipramine. At the 24-month follow-up, the proportion of patients continuing on the original antidepressant was roughly 35% for fluoxetine and 10% to 15% for imipramine and desipramine. These data suggest a substantial acceptability advantage for the SSRI over the TCAs, at least when patients and prescribers are aware of the identity of the medication. However, the proportion of patients continuing to take any antidepressant medication was approximately equal at 6 months and at all the subsequent evaluations for the three groups. These data suggest that patients who find TCAs unacceptable generally agree to treatment with a second medication. Rates of symptoms and quality of life showed similar improvement at all time points, although some evidence was found at or near the trend level for the fluoxetine group to be slightly more improved at the 1-month time point only. These data indicate that the clinical outcomes in actual practice are essentially equivalent whether patients are initially assigned to an SSRI or a TCA. If average improvement is slightly faster when an SSRI is the initial choice, perhaps because fewer patients switch and start over, any difference is no longer apparent at 3 months or thereafter.

Among patients remaining on the initial antidepressant at 1 month, adverse effects were significantly lower in the group assigned to fluoxetine. The method of measurement of adverse effects is not described in detail. Differences in adverse events between the groups were not reflected in the measures of quality of life.

Cost-of-treatment data showed, as expected, that antidepressant medication costs were roughly double for the group initially assigned to fluoxetine (\$217 vs. \$97 for imipramine and \$123 for desipramine during the first 6 months and \$609 vs. \$324 for imipramine and \$376 for desipramine for the entire 24 months). Outpatient costs and inpatient medical and inpatient psychiatric costs were lower, although not significantly so, in the fluoxetine group (\$1,750 vs. \$2,008 for imipramine and \$2,238 for desipramine during the first 6 months and \$6,092 vs. \$6,459 for imipramine and \$6,381 for desipramine for the entire 24 months). These effects resulted in total direct costs across the groups that were not significantly different.

In this study, clinical outcomes were almost identical, whether patients were prescribed fluoxetine or a tricyclic first, when patients were permitted to switch medications freely. Patients who found tricyclics unacceptable generally agreed to treatment with a second medication and “caught up” in terms of clinical outcome. The newer medication “broke even” on costs, in that the higher acquisition costs of fluoxetine were balanced by the lower costs of other services, but did not result in an overall savings to the health care system. On the other hand, a formulary policy of requiring failure of a tricyclic before access to the newer medication was granted would not have saved money in this particular primary care practice. The authors concluded that

the data provide no clear guidance in the initial selection of antidepressant medications and that patient and physician preference therefore provide an appropriate basis for treatment selection.

Interestingly, this group conducted a retrospective database analysis of patients during a similar period of time who did not participate in the randomized trial (47). Reassuringly, the cost-effectiveness results (Table 78.6) were very similar to those from the randomized study.

In the discussion, the authors point out that these conclusions may not apply to other practices. In particular, similar studies in psychiatric specialty practices are needed. The depression of patients in psychiatric specialty practices is generally more severe, and the consequences of delay in treatment response related to a need to switch medications and start over may be more worrisome.

The second randomized prospective antidepressant cost-effectiveness study was conducted in a primary care setting in France (2). Outpatients meeting DSM-IV criteria for major depression were randomized to sertraline (50 to 150 mg/d;  $N = 122$ ) or fluoxetine (20 to 60 mg/d;  $N = 120$ ) in double-blinded fashion for 6 months. Both groups improved significantly from baseline on measures of symptoms and quality of life, and analyses comparing the groups showed no significant differences; however, patients treated with fluoxetine utilized more medical resources. Analyses comparing groups in regard to work and productivity losses were not significant. Cost comparisons (converted to dollars) from the societal perspective favored sertraline over fluoxetine (\$1,551 vs. \$1,735), but neither the variability within groups nor statistical significance of the comparisons was reported.

## COSTS OF AVERTING SUICIDE

Suicide is fortunately a fairly rare event, even in depressed patients (48,49). As a result, many cost-effectiveness studies have not included a consideration of suicide. We touch on the issue only briefly.

The relative safety of the newer antidepressants in overdose is well-known. The use of SSRIs is associated not only with fewer deaths from antidepressant overdose but also with reduced costs of treating overdose (50–52)

Despite clear reductions in mortality from overdoses with the newer medications in comparison with TCAs (53), controversial data from a general practice research database involving 4 million residents of the United Kingdom indicated the rate of death by suicide in patients receiving fluoxetine to be no lower than the rate of death by suicide in patients receiving TCAs (54). Fluoxetine-treated patients appeared to substitute violent methods or carbon monoxide poisoning for overdoses. Such complete method substitution would suggest that SSRIs do not save lives and that saving lives cannot therefore be used to justify their added

expense. These data, however, are based on only 11 suicides among a limited number of fluoxetine cases.

Freemantle et al. (55) modeled the cost per life year saved and cost per life saved that would result from the routine first-line use of SSRIs rather than TCAs in general practice in the U.K. in comparison with current U.K. practice patterns. This analysis produced a very wide range of estimates, primarily because of uncertainty regarding whether SSRI-treated patients would substitute other methods of suicide for overdoses. As part of a simulation, another study included suicide as part of the cost of treatment dropout (56). However, the expert panel estimates of suicide rates in this latter study were very high, and few costs were considered in the analysis.

Whether newer antidepressants do in fact save lives is crucial in a consideration of their cost-effectiveness. More data are needed about the extent to which patients, knowing that the pills are not lethal, might substitute methods of suicide that are even more deadly than TCA overdoses. However, recently emerging epidemiologic data appear to suggest that newer antidepressants may have a favorable impact on death by suicide when all methods, not just overdoses, are taken into account (57–60).

## CONCLUSION

The available data that may be confidently brought to bear on the two cost-effectiveness questions posed in the introduction are surprisingly sparse. Only two prospective randomized studies have been carried out, both in primary care. More prospective studies are clearly needed. Most of the retrospective studies and the simulations contain methodologic limitations sufficient to generate significant concern about their conclusions. Additionally, the studies include diverse variations in almost all the elements of cost-effectiveness analysis, so that cross-comparisons and aggregate conclusions are very difficult to make. However, if we must draw conclusions from the current data, we would suggest the following tentative conclusions.

Based on the limited evidence available, the provisional summary from this review regarding our first question, “Are newer antidepressants cost-effective as first-line treatment from the health care system perspective?” is that first-line use of the newer antidepressants within primary care practice in the United States may be roughly equally effective and also cost-neutral in terms of direct medical resource costs to the health care system. The recently published long-term data from the only randomized study support this view (26), and the simulations and retrospective studies, with all their limitations, do not contradict it. However, because the data are sparse and contain multiple methodologic problems, health care organizations or systems feeling the pinch of the high acquisition costs of the newer medications would be well advised to conduct their own randomized studies.

This is especially true for psychiatric practices and for practices in countries other than the United States.

The data for the primary care treatment of depression are sparse, but those for the cost-effectiveness of the newer antidepressants in psychiatric practice are even more scarce. No randomized studies have been published, and few of the simulations and none of the administrative database studies focus exclusively on psychiatric practice. Many features distinguish the treatment of depression in primary care from the treatment of depression in psychiatric practice, and these could potentially lead to different conclusions about cost-effectiveness. For example, the direct costs of treatment failure may be higher in psychiatric practice than in primary care (61), and this consideration would favor the cost-effectiveness advantages of the better tolerated newer agents. On the other hand, the tendency of psychiatrists to use higher and possibly more effective doses of TCAs than primary care prescribers do would likely favor the cost-effectiveness of TCAs over SSRIs in psychiatric practice. Similarly, it may be less likely in psychiatric practice than in primary care that the greater tolerability of SSRIs and the reduced requirement for dose titration would offset costs by decreasing the need for outpatient visits; for depressed patients in psychiatric practice, with relatively severe depression and higher levels of comorbidity, frequent visits may be necessary independently of these considerations to monitor for increased suicide risk. Prospective randomized cost-effectiveness experiments in psychiatric practice could address the substantially different environment of specialty mental health care.

Similarly, although the data on the treatment of depression in the United States are limited, those on the cost-effectiveness of the newer antidepressants in other countries, especially developing countries, are still more limited. No randomized studies outside the United States have compared newer and older antidepressants. Some of the simulations and none of the administrative database studies focus on other developed countries, such as Canada and the European nations. The many ways in which the treatment of depression differs across countries and economies could potentially lead to different conclusions about cost-effectiveness (62). Acquisition costs for the newer medications are generally lower in countries other than the United States (63). Nevertheless, price may still put the newer antidepressants out of reach for most of the population in some developing countries (64). The organization of health care systems varies greatly, and the potential of the newer antidepressants to offset costs could also vary greatly across countries. Prospective randomized cost-effectiveness experiments in countries other than the United States would make it possible to evaluate whether cost-effectiveness conclusions are widely applicable.

The second question we posed in the introduction was, “Are newer antidepressants cost-effective as first-line treatment from the global societal perspective?” This perspective

includes *all* costs and *all* health effects. Fewer studies have attempted to address societal indirect/productivity costs, and none of the studies is prospective. Indirect/productivity costs were not comprehensive in some studies, being limited to family burden or absence from work. In the studies reporting QALYs, the outcome rates were taken from expert opinion panels, or utility determinations were uncertain. Most of these studies have numerous other methodologic limitations. Better studies are needed, particularly on the substitution of suicide methods, enhancement of work productivity, and reduction of absenteeism and family burden. However, if the newer antidepressants are in fact health care resource cost-neutral in the health care system, the chance is significant that the newer antidepressants are cost-effective in society. Health care system health resource cost neutrality clearly suggests similar cost neutrality in total health resource costs to society because the total health care resource costs to society also are borne by the health care system. It is likely that society reaps benefits not seen from the health care system perspective, including decreased use of informal caregiver time, decreased use of patient time, and perhaps decreased use of resources other than health care resources, in addition to positive changes such as increased productivity.

Lastly, as newer antidepressants begin to come off patent, their cost eventually should go down as a result of generic competition. When this occurs, the cost-effectiveness of the newer medications will increase (45).

## DISCLOSURE

Dr. Woods has received honoraria from Janssen Pharmaceutica and Wyeth-Ayerst Pharmaceuticals for speaking engagements and invited publications.

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