DEPRESSION AND ANXIETY, VOLUME 12, SUPPLEMENT 1:102–109 (2000)

PHARMACOECONOMIC STUDIES OF ANTIDEPRESSANTS: FOCUS ON VENLAFAXINE

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Newer antidepressants are more expensive in terms of acquisition costs than older drugs. However, cost effectiveness simulations and retrospective analyses of administrative databases of newer antidepressants, including venlafaxine, suggest that the higher acquisition costs may be offset or more than offset by savings of other treatment costs. Because simulations and retrospective studies are vulnerable to multiple methodologic uncertainties, large scale randomized "real-world" cost effectiveness experiments are needed. If venlafaxine in actual practice is more effective or has a more rapid onset of action than SSRIs as suggested by efficacy studies and existing meta-analyses, these effects could translate into pharmacoeconomic advantages. Depression and Anxiety, Volume 12, Supplement 1:102–109, 2000. *© 2000 Wiley-Liss, Inc.*

Key words: *cost effectiveness simulations; new antidepressants; acquisition costs*

INTRODUCTION

Depression exacts a terrible toll on its sufferers and their families, workplaces, and communities. The World Health Organization determined that depression was the fourth leading cause of global disease burden in 1990 and projected that it would be the second leading cause by 2020 [Murray and Lopez, 1996]. Costs of depression to society as a result of lost productivity due to morbidity and mortality have been estimated at $14.2 billion (in 1980) [Stoudemire et al., 1986] and $31.3 billion (in 1990) [Rice and Miller, 1995] in the United States. Moreover, direct treatment costs for depression, exclusive of medication acquisition costs, have been estimated at $2.0 billion (in 1980) [Stoudemire et al., 1986] and $11.2 billion (in 1990) [Rice and Miller, 1995] in the United States.

Since 1985, several new antidepressants have been introduced into practice, including the selective serotonin reuptake inhibitors (SSRIs) fluoxetine (1987), sertraline (1991), paroxetine (1992), and citalopram (1998), and 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). Each newer antidepressant is more expensive in terms of acquisition costs than the older generation of tricyclics, heterocyclics, and monoamine oxidase inhibitors.

Given that their higher acquisition costs are higher than those of the older drugs, it is of particular interest whether the new, more expensive medications are cost effective as first-line treatment, relative to the less expensive drugs. The newer medications could theoretically be cost effective relative to less expensive drugs if the newer medications are associated with benefits over and above those of the older medications that outweigh the higher acquisition costs. It is also important to determine whether any of the newer antidepressant medications could be cost effective relative to others of the newer medications.

In order to address cost effectiveness, it is crucial to pay attention to who is paying which costs and who is receiving which benefits. The analysis must require that the same person or group of people are both bearing the costs that are considered in the analysis and receiving the benefits that are considered in the analysis. This person or group of people is then referred to as the "perspective" of the analysis. Various perspectives are possible, including a patient perspective, a family perspective, an employer perspective, a health care system perspective, or a society perspective. In practice, most studies have taken one of the latter two perspectives.

The present article will concern itself with the cost effectiveness of one of the newer medications: the dual action serotonin and norepinephrine reuptake inhibitor venlafaxine. Evidence bearing on its cost effectiveness relative to the older generation drugs will be presented, as well as evidence bearing on its cost effectiveness relative to SSRIs and other newer antidepres-

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sants. This evidence generally comes from studies that may be grouped into four methodologies: efficacy meta-analyses, cost effectiveness simulations, retrospective analysis of administrative databases, and prospective cost effectiveness experiments. Each of these are addressed in turn.

EFFICACY AND TOLERABILITY META-ANALYSES

Apart from acquisition costs, the remaining costs and benefits that combine to determine cost effectiveness are influenced by the efficacy and tolerability of the treatment, as expressed in the actual practice under consideration. Since the acquisition costs of venlafaxine and other newer antidepressants appear to be in the same ballpark, issues of comparative efficacy and tolerability of venlafaxine relative to other newer antidepressants are relevant to the cost effectiveness of venlafaxine.

Numerous meta-analyses of randomized short-term SSRI vs. TCA trials suggest that the efficacy of these two classes of antidepressant is quite similar and that the SSRIs have a small but consistent tolerability advantage [Anderson, 1998, 2000; Anderson and Tomenson, 1995; Bech et al., 2000; Geddes et al., 2000; Hotopf et al., 1997; Montgomery et al., 1994; Mulrow et al., 1998, 2000; Song et al., 1993; Steffens et al., 1997; Trindade et al., 1998; Williams et al., 2000].

Depression encompasses a spectrum of severity. At one end of the spectrum lie less severely ill patients that are managed almost exclusively as outpatients, often in the general health care sector, and that probably include some cases of what is currently termed generalized anxiety disorder. At the other end of the spectrum lie more severely ill cases that frequently require psychiatric hospitalization and often include melancholia or even psychosis. Recently, several randomized studies have been published directly comparing venlafaxine to SSRI or with buspirone across this severity spectrum (Table 1). Many of these studies have been published relatively recently and have yet to be included in meta-analyses. Generally the evidence in Table 1 suggests that venlafaxine, perhaps related to its dual mechanism of antidepressant action, may be associated fairly consistently across the depression severity spectrum with a more rapid therapeutic benefit and/or a higher rate of remission than SSRIs or buspirone. One additional study appears to have found venlafaxine similar in efficacy to fluoxetine in depressed primary care patients [Tylee et al., 1997]. Many of the study samples sizes in Table 1 do not yield high power to detect the relatively small effect size differences expected between active treatments. As a result, some of the significant differences in Table 1 are not always consistent across measures, subgroups, or timepoints. Therefore this evidence must be interpreted with caution.

The available meta-analyses, however, are generally consistent with these conclusions. Early studies were included in the US Agency for Healthcare Research and Quality (AHRQ) commissioned antidepressant meta-analysis [Mulrow et al., 1998]. This analysis included four studies that compared venlafaxine to TCAs for depression. The venlafaxine comparisons to TCA were similar to the SSRI comparisons to TCA. Another recently published meta-analysis included one of the four studies from the AHRQ report and two others comparing venlafaxine to trazodone and

TABLE 1. Randomized active comparator studies of venlafaxine in depression spectrum disorders

						Selected findings[b]	
Study[a]	Depression spectrum	Cell N	Dur	VEN	Comparator	Rapidity	Remission
1	GAD	91	8 w	XR	buspirone	XR>B 2w	nr
2	outpatients	na	na	XR	buspirone	na	na
3	Anxiety/depression	120	12w	XR	fluoxetine	XR≈F	XR≈F
4	Depression/dysthymia	42	24w	V	paroxetine	V>P 6w	V>P
5		157	8 w	V	fluoxetine	V>F 3w	nr
6		72	8 w	V	fluoxetine	V≈F	nr
7	Depressed	191	8 w	V	fluoxetine	V≈F	V>F
8	outpatients	156	6 w	V	fluoxetine	V≥F 1w	nr
9		100	8 w	XR	fluoxetine	XR>F 3w	XR>F
10		98	8 w	V	sertraline	V>S 6w	V>S
11	Resistant depression	61	4 w	V	paroxetine	nr	V>P
12	Depressed	34	6 w	V	fluoxetine	V>F 4w	nr
13	inpatients	54	6 w	V	fluoxetine	V≈F	V≥F
14	Delusional depression	14	6w	V	fluvoxamine	V≈F	V≈F

[a]*Citations. 1: Davidson et al., 1999. 2: Rolland et al., 2000. 3: Silverstone and Ravindran, 1999. 4: Ballus et al., 2000. 5: Dierick et al., 1996. 6: Diaz-Martinez et al., 1998. 7: Costa e Silva, 1998. 8: Rudolph et al., 1998. 9: Rudolph and Feiger, 1999. 10: Mehtonen et al., 2000. 11: Poirier and Boyer, 1999. 12: Clerc et al., 1994. 13: Tzanakaki et al., 2000. 14: Zanardi et al., 2000.*

[b]*Selected among multiple measures, subgroups, and/or timepoints; for rapidity of effect onset, time point of earliest significant difference is shown; nr, not reported; na, not available.*

fluoxetine [Srisurapanont, 1998]. The odds ratios for venlafaxine were higher than 1.0 for response and lower than 1.0 for tolerability in each of these three studies. A recent meta-analysis of depressed patients treated with venlafaxine XR reached similar conclusions [Einarson, 1999]. Since this meta-analysis sampled many studies that included only venlafaxine XR arms, or only SSRI arms, the comparison is somewhat indirect and therefore must be interpreted with caution. The analysis included 44 trials with 63 study arms and 4,033 patients. Therapeutic success was defined as a 50% decrease in the HAM-D or MADRS score. Venlafaxine XR showed a 73.7% success rate, significantly higher than that for the studied SSRIs (61.1%) and TCAs (57.9%).

COST EFFECTIVENESS SIMULATIONS

Pharmacoeconomic simulations construct mathematical models of practice based on decision analysis. Each important outcome is identified and assigned a probability value and utility (costs and/or benefits) values. Typically these values are derived from meta-analyses or literature reviews or, when other means of obtaining estimates are not available, from "delphic" panels: a consensus opinion from a panel of experts. More than a dozen such simulations comparing SSRIs to TCAs have been published. These simulations were reviewed in 1997 [Woods and Baker, 1997] and again recently [Woods and Baker, in press].

In general these simulations have concluded that SSRIs were likely to be cost effective relative to TCAs, although there have been exceptions [Canadian Coordinating Office for Health Technology Assessment, 1998; McFarland, 1994; Stewart, 1994; Woods and Rizzo, 1997]. A number of methodologic limitations, however, affect the interpretation of the simulation results. As an example, consider one early simulation that was influential in that it provided a template subsequently modified by several other research groups [Jonsson and Bebbington, 1993, 1994]. The cost effectiveness of the SSRI paroxetine was compared to that of the TCA imipramine over 1 year, based on calculations of cost per treated patient and cost per successfully treated patient. The model provided for patients who fared poorly on the initial antidepressant to be switched to the alternative treatment but failed to allow for the possibility that the switched treatment could be successful. The durations of maintenance treatment were short relative to practice guidelines, and the initial success rates for paroxetine were unrealistically high compared to meta-analytic estimates. Each of these model parameter estimates tended to drive the simulation in favor of the SSRI, and when these assumptions were revised, the model suggested that imipramine could be more cost effective than the SSRI as first line treatment [Woods and Rizzo, 1997].

Several decision analytic simulations of the cost effectiveness of venlafaxine have been published. In the first publication [Einarson et al., 1995], two simulations were derived: one for outpatient starts and one for inpatient starts. Each simulation compared initial treatment with venlafaxine to initial treatment with SSRIs, TCAs, and heterocyclic antidepressants (HCAs) over 300 days based on the cost of treatment per symptom free day achieved. "Symptom free days" were calculated from the initial success rates and long-term success rates based on the authors' meta-analysis of 34/221 studies that met their criteria and data on file. Among TCAs, studies of amitriptyline and imipramine were included, and among SSRIs, studies of fluoxetine and paroxetine were included. For outpatient antidepressant starts, the rank order cost effectiveness was HCAs > venlafaxine > SSRIs > TCAs; for inpatient starts, the rank order was venlafaxine > HCAs > TCAs > SSRI. Based on an expert panel, costs for two cardiologist visits, four TCA blood levels, and three electrocardiograms per TCA patient were built in to the model.

In the second venlafaxine study, Priest [1996] summarized a cost effectiveness analysis, conducted by Gross, on the effect of substituting venlafaxine for fluoxetine in hospitalized patients. The simulation provided for venlafaxine being 20% more effective than fluoxetine and equally safe. Venlafaxine was reported to cost 11% less per episode of major depressive disorder.

In the third venlafaxine study, a 6 month model was constructed by using an expert panel of three psychiatrists and three family physicians, taking the perspective of the Ontario Ministry of Health. Two models, one outpatient and one inpatient, compared initial starts with venlafaxine, SSRIs, and TCAs. Model values for treatment success and drop outs were derived from a meta-analysis, using data from double-blind randomized trials comparing any two of the following drugs of interest: venlafaxine, amitriptyline, imipramine, desipramine, nortriptyline, fluoxetine, sertraline, paroxetine, or fluvoxamine. Costs per successfully treated outpatient in 1996 Canadian dollars were $6044, $6633, and $9035 for venlafaxine, SSRIs, and TCAs, respectively, and $17,235, $20,874, and $20,479 for inpatients. Venlafaxine showed a similar advantage over SSRIs and TCAs when cost per symptom free day was modeled. When marginal cost effectiveness was calculated, venlafaxine was dominant over the other two drugs classes, meaning that effectiveness was higher while costs were lower. Outpatient results for venlafaxine vs. TCAs were relatively insensitive to variation in the success rate parameters used in the model, but when the lower 95% confidence limit for success rate was substituted for venlafaxine and the upper 95% confidence limit was substituted for SSRIs, SSRIs dominated over venlafaxine. Both venlafaxine vs. TCA and venlafaxine vs. SSRI results were sensitive to success rate estimates for inpatients.

RETROSPECTIVE ANALYSES OF ADMINISTRATIVE DATABASES

In the last few years, numerous retrospective cost effectiveness analyses of antidepressant administrative databases have appeared [Croghan et al., 1997, 2000; Crown et al., 1998; Forder et al., 1996; Griffiths et al., 1999; Hylan et al., 1998; Melton et al., 1997; Russell et al., 1999; Sclar et al., 1994, 1995, 1998, 1999; Simon and Fishman, 1998; Singletary et al., 1997; Skaer et al., 1995; Smith and Sherrill, 1996; Sullivan et al., 2000; Thompson et al., 1998]. These studies were reviewed in 1997 [Woods and Baker, 1997] and again recently [Woods and Baker, in press].

Only one of these studies investigated the cost effectiveness of venlafaxine. The remaining studies are relatively evenly balanced in concluding that costs of health care are either significantly lower or similar after SSRI treatment than after TCA treatment [Woods and Baker, in press].

While the prospective trial is the gold standard, such trials are costly to perform and require several years to return an answer to the question. Retrospective studies are less expensive and can be conducted more quickly. These administrative database studies also have the clear advantage of external validity.

Unfortunately, however, there are a number of disadvantages with this approach. As a consequence of the database employed, these studies are generally unable to determine effectiveness of treatment. As the result, these studies tend to assume a worst case of equivalent outcome between newer antidepressants and older agents and among newer antidepressants and then define the more cost effective care as the treatment associated with lower overall healthcare costs. In addition, a number of methodologic issues complicate the interpretation of these studies . Since patients are not randomly assigned to treatment, it is likely that the constructed groups may not be comparable in some important way at baseline. This is termed "selection bias." The statistical analysis of these administrative databases is becoming increasingly sophisticated, but no currently available statistical technique can completely control for possible selection biases across treatment groups that could affect conclusions. In some studies costs analyses are restricted to those that are "depression-related," raising questions about the accuracy of the identification of depression relatedness of specific visits and procedures. Some of the studies appear to neglect to correct for baseline health care expenditures.

Moreover, the possible impact of a "cohort effect" is only beginning to be investigated. The term "cohort effect" is used to indicate the possibility that the distribution of starts of different antidepressants could differ over time within the study interval [Woods and Baker, 1997, 1999]. If costs of care are also changing over time within the study, perhaps as the result of secular effects such as those potentially caused by managed care [Frank and Brookmeyer, 1995; Goldman et al., 1998], the assessment of the effects of antidepressant selection on costs of care could be confounded. Recent studies have included time of the antidepressant start within the study interval as an explanatory variable in the analysis but appear to have restricted attention to its effect on initial selection of antidepressant. No study shows data that indicates whether health care costs associated with antidepressant starts were increasing or decreasing during the study interval or how this secular cost trend if present may have interacted with the distribution of starts of individual antidepressants over the study interval.

Similarly, the effects of a possible "launch bias" have also only begun to be investigated. Launch bias [Croghan et al., 2000] is a type of selection bias that may result in a different sort of patient being prescribed a new antidepressant in the early years after its launch than after the medication has been on the market for several years. It is possible that patients selected by their prescribers to receive a brand new antidepressant may on the average 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 the average be 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 that have attempted to control for previous treatment have eliminated patients who have received antidepressants in the 4 to 6 months prior to the index antidepressant start. Although this exclusion is somewhat reassuring, it still does not prevent patients from being included in the analysis who were already being prescribed an antidepressant at the start of the study interval, then stopped antidepressant therapy for 4 to 6 months, perhaps related to ineffectiveness, and then restarted a different, more recently launched, antidepressant that was identified as the index start. 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 such patients can be included in the analysis, a launch bias could exist that would be unfavorable to the more recently launched antidepressant. Some studies have attempted to control for treatment resistance by restricting attention to "single episode" depressed patients. This restriction was intended to reduce the possibility of a selection bias if patients chosen to receive to the newest medications were more refractory as a group than patients chosen to receive more established medications. This possibility may still have influenced analyses comparing the first three SSRIs to market [Sclar et al., 1995], because in subsequent studies some patients with "single episode" depression

were found to have had previous episodes treated by antidepressants [Sclar et al., 1998, 1999].

Venlafaxine has been included in one administrative database cost effectiveness study, with results of an initial publication [Griffiths et al., 1999] being extended [Sullivan et al., 2000]. This research investigated the cost effectiveness of venlafaxine as a second line alternative after SSRI failure in nine individual health care plans affiliated with a national managed care organization from 1993 to 1997. In the first report, patients had to have received 2 months of SSRI prior to switching to at least 2 months of either venlafaxine or a TCA. In the extension report, patients had to have received first line treatment with any antidepressant for 2 months prior to switching to an antidepressant treatment of a different class for at least 2 months.

In the first report, 188 patients received venlafaxine and 172 received TCAs. Venlafaxine patients were significantly younger and had suffered from significantly less medical illness comorbidity and had incurred significantly lower treatment costs in the 6 months prior to baseline. A significantly higher proportion of venlafaxine prescriptions were written by psychiatrists. In univariate analyses, both depression-coded and nondepression-coded costs over the next 12 months were significantly lower for the venlafaxine group; however, after adjustment for potential confounding baseline variables, the two groups did not differ significantly for any cost category.

In the extension report, 208 patients were switched to venlafaxine, and 332, 191, and 250 patients received SSRIs, TCAs, and other antidepressants as second line treatment, respectively. Baseline differences and univariate and multivariable cost results were generally similar to those from the initial study. Venlafaxine and SSRI patients remained on continuous second line treatment longer (7.6 and 7.8 months) than patients taking TCAs or other antidepressants (5.9 and 6.7 months). Because this study investigated venlafaxine as a second line treatment in comparison to other medications chosen as second line, considerations of possible launch bias probably do not affect interpretation of these results.

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. The randomization permits the investigator to ascribe any observed cost effectiveness difference 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 different in some important way? Relatively little attention has been paid to this issue in depression research, although one study found that patients participating in a randomized depression trial had significantly fewer co-morbid diagnoses than excluded patients and were more likely to be single episode patients [Partonen et al., 1996].

At present, only two prospective pharmacoeconomic studies examining the cost effectiveness of newer antidepressant treatments have been published, and no such study has been conducted with venlafaxine. The first study was a randomized controlled trial designed to investigate a health policy question: What are the cost and health outcome consequences in actual practice of a decision to use an SSRI vs. a TCA as first-line drug treatment for depression? The initial report from this study included data up to the 6 month point after randomization. Patients were followed for 2 years after randomization, and the long-term data have been reported recently . Patients were enrolled from participating primary care clinics in a large U.S. health maintenance organization. Patients were randomly assigned to receive the prototypical SSRI fluoxetine (n=173) or the commonly prescribed TCAs imipramine (n=182) or desipramine (n =181). After randomization had occurred, patients were free to switch antidepressants. Evaluators but not patients or prescribing physicians were blinded to the initial treatment assignment.

At the 6 month time point, the proportion of patients continuing on the original antidepressant was nearly 60% for fluoxetine, less than 40% for imipramine, and approximately 30% for desipramine. By the 24 month time point, the proportion of patients continuing on the original antidepressant was roughly 35% for fluoxetine and 10–15% 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 and there is no financial disincentive for patients to switch. However, the proportion of patients continuing to take any antidepressant medication was approximately equal at the 6 month and all subsequent time point for the three groups. These data suggest that patients who find TCAs unacceptable generally agree to treatment with a second medication. Symptom and quality of life ratings showed similar improvement at all time points, although there was some evidence 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.

Total direct costs across the groups were not significantly different.

The second randomized prospective antidepressant cost effectiveness study was conducted in a primary-care setting in France [Boyer et al., 1998]. Outpatients meeting DSM IV criteria for major depression were randomized to sertraline (50 to 150 mg/day; n = 122) or fluoxetine (20 to 60 mg/day; n = 120) in double-blind fashion for 6 months. Both groups improved significantly from baseline on clinical and quality-of-life measures, and analyses comparing the groups showed no significant differences; however, patients treated with fluoxetine utilized more medical resources. Analyses comparing groups on work and productivity losses and cost comparisons were not significant.

CONCLUSIONS

Despite a rapidly growing literature, more research is needed on the relative cost effectiveness of SSRIs vs. the older agents. Almost all of the studies are either simulations or retrospective analyses. Although the majority of the existing simulations appear to support the cost effectiveness of SSRIs, several methodologic issues diminish confidence in these results. In particular, very few of the simulations model treatment for more than 1 year, and longer model durations would appear to favor medications with lower acquisition costs. The retrospective administrative database analyses all suggest that the higher acquisition costs of SSRIs are either offset or more than offset by other cost of treatment savings. Unfortunately, however, all of these studies appear to be vulnerable to a cohort effect in that the average patient starting on TCA included in the analysis would appear to have started earlier in the study interval than the average patient starting an SSRI. Thus the apparent treatment effect may be confounded by a secular trend.

More research is needed on relative cost effectiveness across the newer antidepressants as well. Again, almost all of the studies are simulations or retrospective database comparisons. Many of the retrospective cost comparisons among the SSRIs may have been affected by a specific type of selection bias that may be termed "launch bias."

For each of these questions, large-scale randomized "real-world" cost effectiveness experiments are needed. Only two such studies exist currently. These studies suggested that the SSRI and TCAs employed were equally cost effective [Simon et al., 1996, 1999] and that the two SSRIs employed also were equally cost effective [Boyer et al., 1998]. Because both of these studies were conducted in primary care practice, randomized cost effectiveness experiments are particularly needed in psychiatric practice.

Studies with venlafaxine employing this design are needed as well. If venlafaxine in actual practice is more effective or has a more rapid onset of action than SSRIs as suggested by efficacy studies and existing meta-analyses, these effects could translate into pharmacoeconomic benefit. In hospitalized patients, a speed of onset advantage for venlafaxine could lead to a length of stay (LOS) advantage for the index hospitalization. Another important pharmacoeconomic benefit of venlafaxine could be effects on work. Multiple studies demonstrate that depression is associated with absenteeism from work and diminished productivity while at work [Claxton et al., 1999; Judd et al., 2000; Kessler et al., 1999; Mintz et al., 1992; Zhang et al., 1999]. If venlafaxine is more effective or has a more rapid onset of action, this may translate into a more rapid and/or more frequent return to work after hospital discharge. In outpatients, more rapid response and a higher rate of remission could lead to fewer days lost from work and better productivity while at work. Employers as purchasers of health care services would favorably view any such workplace benefits of an antidepressant.

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