Antidepressants in the Medically Ill: Diagnosis and Treatment in Primary Care

Wayne Katon and Peter P. Roy-Byrne

Major depression is one of the most common clinical problems seen by primary-care physicians. The prevalence is 5% to 10% in primary-care outpatients and 15% in medically ill inpatients. Despite this high prevalence rate, depression is frequently not accurately diagnosed. Evidence suggests that misdiagnosis often occurs because patients with depression frequently focus preferentially on somatic complaints or amplify complaints of chronic medical illness. The tricyclic antidepressants are more effective than placebo, both in treating medically ill patients with depression and primary-care patients with major depression. Common side effects of the tricyclic antidepressants such as the anticholinergic, cardiac, and blood-pressure problems are reviewed, with emphasis on the use of specific tricyclics in medically ill populations.

In 1978, Regier et al. (1) reported that 50% to 60% of patients with mental illness in the United States were treated exclusively within the primary medical care system. These findings were confirmed in the recent Epidemiologic Catchment Area (ECA) study validating the label of primary-care medicine as the "de facto" mental health center of the United States (2). During a six-month period, 70% of patients with mental illness in the ECA study were seen in primary care, whereas only 20% made a visit to a mental-health professional (2).

A large computer-based study of >50,000 patient visits to 188 primary-care physicians in Virginia determined that anxiety and depression accounted for 87% of the psychiatric illnesses seen in primary care (3). The more severe illnesses such as schizophrenia, manic depressive illness, and dementia are preferentially referred to the mental health center.

Our purpose here is to review studies of the epidemiology, phenomenology, and recognition of depression in primary care, as well as the studies of the use of tricyclic antidepressants in treating medically ill populations with major depression. In addition, common side effects of tricyclic antidepressants will be reviewed, with a careful focus on recommendations for use of specific tricyclics within medically ill populations (such as patients with cardiac illness).

Prevalence of Depression in Primary Care

Several recent large epidemiological studies in the United States have demonstrated that 3% to 4% of people in the community suffer from major depression (4, 5), but only a third of them are receiving treatment for their condition. Others (4, 6, 7) have demonstrated that patients with depression make significantly more visits to physicians than do nondepressives. Moreover, Katon et al. (7) demonstrated that these patients had significantly more medical tests than nondepressives, thus increasing medical costs.

Table 1 summarizes results of 11 studies that sought to estimate the prevalence of depression in primary-care pa-

tent populations. In four studies (8-11), structured psychiatric interviews (the SADS-L (12), DIS (13), PSE (14)) and operational criteria (Research Diagnostic Criteria (15) or DSM III (16) were used. In the rest, self-rating scales were used (7, 17-22): the Beck Depression Inventory (BDI) (23), the Zung Self-Rating Depression Scale (SDS) (24), the HSCL (25), and the new NIMH Depression Self-Rating Scale (CES-D) (26). The depression self-ratings scales are highly sensitive but not very specific. Thus they can be used to identify most patients with major depression, but they also select false positives who meet criteria for depression on the self-rating scales but have other primary disorders such as alcohol abuse, bereavement, terminal medical illness, dysthymic disorder, or schizophrenia. The studies that utilized depression self-rating scales yielded prevalence rates between 12% and 25% (7, 17-22). The four studies in which structured psychiatric interview and operational diagnostic criteria were used yielded a prevalence rate of 5.0% to 10% among primary-care outpatients (8-11). This represents a substantial rate as compared with 5.7% for hypertension, the most common medical condition seen in primary-care settings (3). Moreover, according to recent studies, at one-year follow-up approximately half of primary-care depressives are still ill (27, 28), contradicting the notion that depressives seen in general practice have mainly transient distress.

Accuracy of Diagnosis of Depression in Primary Care

Particularly disturbing is the high rate of misdiagnosis of depression in primary-care populations. Four studies in which high cutoff scores on depression-rating scales were used to identify depressed patients all found that most cases of depression were missed by physicians, the respective miss rates being 96%, 82%, 61%, and 50% (7, 18, 19, 29). Although these findings are limited by this method of diagnosis, a recent study in which a structured interview was used confirmed these findings, reporting that 74% of cases of depression were missed (9). Moreover, in two of the above studies, accuracy of diagnosis did not improve with increasing severity of depression; the misdiagnosis rate was equally high in the severely depressed group (18, 29). In agreement with these findings, Weissman et al. (4) demonstrated that 65% of patients with major depression in a community sample did not receive specific treatment for their illness; half of the depressed group had been prescribed sedative-hypnotics for insomnia and anxiety, and only 17.2% had been specifically treated with antidepressant medication.

Reason for Misdiagnosis of Depression

Goldberg and Bridges (30, 31) found that >50% of patients with depression and anxiety in three large family-practice clinics presented initially with a somatic complaint. Retrospective studies (4, 6, 32, 33) suggest that depressed patients have significantly more clinic visits and hospitalizations during the months preceding the diagnosis of de-
pression and that the presenting problems typically consisted of ill-defined "functional" complaints, pain with no apparent organic origin, and "nervous" complaints such as increased tension and anxiety.

Because of the limitations of the previous retrospective studies, Katon et al. (7) prospectively screened 147 primary-care patients for depression by means of the BDI (short form) (23) and the SDS (24). Forty percent of the depressed patients were also screened with a structured psychiatric interview. Patients with moderate to severe depression were then compared with patients without depression by prospectively monitoring their use of the clinic during one year, as well as auditing their charts for clinic use during the two years preceding the screening. Confirming earlier studies, patients with depression visited the physician more frequently, made more telephone calls to their physicians, and had more medical evaluations than the nondepressed control group in the year after screening. They were also more likely to have nonspecific or vague complaints, psychophysiological complaints, and depressive complaints than were controls.

Pain Complaints and Depression

Conceptually different, although related to the previous section, complaints of pain represent one of the most frequent types of somatic presentations of depression. Katon and colleagues (34-37), using a structured psychiatric interview (DIS (13)), determined that patients with different types of chronic pain (as well as the aversive symptom of chronic tinnitus) had significantly higher prevalence rates of lifetime and current major depressive episodes than controls (Table 2). As seen in Table 2, these patients tend to have histories of recurrent depression, and 50% of these patients had their first major depressive episode and (or) abused alcohol or drugs before their chronic pain began.

As studied from the opposite perspective, Von Knorrning et al. (38) found that 57% of their sample of psychiatric patients with depression had one or more associated significant pain complaints. A high prevalence of major depression is also seen in many diseases in which pain is prominent, such as diabetic neuropathy, chronic abdominal pain, headache syndromes, atypical facial pain, and cancer associated with chronic pain (39-43). Evidently, not only does major depression frequently precede development of chronic pain, but also major diseases associated with pain syndromes often lead to depression. Lindsay and Wyckoff (44) suggested that we label these syndromes the "depression-pain syndrome" (the implication being that chronic pain and depression are often linked biologically and indeed respond to similar treatments). Certainly results of treatment with tricyclic antidepressants suggest an underlying common neurochemical pathway in depression and chronic pain, in that tricyclic antidepressants have been demonstrated in numerous double-blind trials to be effective in both depression associated with chronic pain (40, 45-52) and chronic pain without associated depression (41, 42, 53-59) (see Tables 3 and 4).

Thus many depressed patients present to their physicians with physical complaints. Because physicians are generally trained to focus preferentially on biological/somatic symptoms, leaving psychological problems as diagnoses of exclusion (60), they often increase these patients' hypochondriacal worries and subject them to the risks of iatrogenic harm through overtreatment of somatic symptoms as well as nontreatment of underlying depression.

### Medical Illness and Depression

The close relationship between depression and chronic or severe medical illness is suggested by the studies of prevalence of depression in various specialized medical groups (heterogeneous samples of medical inpatients and patients being treated for specific medical illnesses). When patients with chronic medical illness develop depression, they often amplify complaints about their illness or regress in their

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref. no.</th>
<th>Prevalence rate(s)</th>
<th>Criteria/Instrument (cutting score in parentheses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salkind (1969)</td>
<td>17</td>
<td>25% depressed</td>
<td>BDI (&lt;17)</td>
</tr>
<tr>
<td>Hooper et al. (1979)</td>
<td>8</td>
<td>5.8% with major depression</td>
<td>SADS-L</td>
</tr>
<tr>
<td>Nielsen &amp; Williams (1980)</td>
<td>18</td>
<td>12.2% mildly depressed</td>
<td>BDI (&gt;13)</td>
</tr>
<tr>
<td>Seller et al. (1981)</td>
<td>19</td>
<td>5.5% moderately depressed</td>
<td>BDI (&gt;17)</td>
</tr>
<tr>
<td>Hankin and Locke (1982)</td>
<td>20</td>
<td>14% definitely depressed</td>
<td>BDI (&gt;21)</td>
</tr>
<tr>
<td>Zung et al. (1983)</td>
<td>10</td>
<td>20% probably depressed</td>
<td>CES-D (&gt;16)</td>
</tr>
<tr>
<td>Peterson &amp; Peterson (1986)</td>
<td>21</td>
<td>13.2% depressed</td>
<td>SDS (&gt;50)</td>
</tr>
<tr>
<td>Katon et al. (1988)</td>
<td>7</td>
<td>10% depressed</td>
<td>DSM III</td>
</tr>
<tr>
<td>Barret et al. (1987)</td>
<td>22</td>
<td>18.3% moderately depressed</td>
<td>SDS (&gt;60)</td>
</tr>
<tr>
<td>Schuberg et al. (1985)</td>
<td>9</td>
<td>9.2% depressed</td>
<td>Combined 16 HSCL depression items and 4 CESD items</td>
</tr>
<tr>
<td>Blacker and Clare (1987)</td>
<td>11</td>
<td>5.0% with major depression</td>
<td>Diagnostic Interview Schedule</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>SADS and PSE</td>
</tr>
</tbody>
</table>

### Table 2. Prevalence Rates of Depression as Related to Pain, Tinnitus

<table>
<thead>
<tr>
<th></th>
<th>Current major depression</th>
<th>Lifetime major depression</th>
<th>No. of episodes</th>
<th>Associated psychiatric and (or) medical illnesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain</td>
<td>33%</td>
<td>57%</td>
<td>3</td>
<td>Alcoholism (34)*</td>
</tr>
<tr>
<td></td>
<td>vs controls</td>
<td>3%</td>
<td>3%</td>
<td>Panic disorder (36)</td>
</tr>
<tr>
<td></td>
<td>34% vs</td>
<td>66% vs</td>
<td>5</td>
<td>Substance abuse, sexual abuse (35)</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>vs controls</td>
<td>10%</td>
<td>5</td>
<td>Mild sensorineural hearing loss (37)</td>
</tr>
<tr>
<td></td>
<td>60% vs</td>
<td>75% vs</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vs controls</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Ref. no. in parentheses.
self-care and monitoring (stop taking medications, gain weight, drink more alcohol) and consequently exacerbate their illness (61, 62).

Two studies have shown that in geriatric patients the most frequent precipitating stress causing depression is physical illness (63, 64). The severity of the medical illness is also a determining factor. In two separate studies (20, 65) the prevalence rate of depression was substantially higher in the more severely medically ill than found in mildly to moderately ill patients (61% vs 21% and 27% vs 13%). Table 5 lists studies examining the prevalence of depression in medical inpatients. Rates vary between 14 and 33%, owing to variations in patient population and method of assessment (in most studies, depression-rating scales were used rather than structured interviews) (66-70).

Depression is a particularly common finding in patients with cancer, and it seems to be related to both severity of illness and inpatient vs outpatient status. In one study of hospitalized oncology patients, 42% met DSM-III criteria for major depression (43) and, in another, one-third of a hospitalized sample with advanced cancer were significantly depressed (71). On the other hand, 6% of outpatients with cancer met DSM-III criteria for major depression (72).

Patients who have recently suffered a stroke appear to be particularly vulnerable to major and minor depression, the respective prevalences being 26% and 24% (73, 74). At the sixth month follow-up, these proportions increased to 34% and 26%. In more than half these patients, depression was strongly associated with left frontal lesions. Moreover, the closer the anterior border of the lesion was to the frontal pole, the more severe was the depression.

Depression is also found frequently in patients with cardiac disease (75). Lloyd and Cawley (76) determined that 19 of 100 male patients whom they interviewed one year after myocardial infarction suffered from depression. The prevalence of depression is also high in other serious medical conditions, e.g., about 37% in spinal cord injury (77) and about 23% to 33% after the onset of end-stage renal disease (78-80). Moreover, Abram (81) has demonstrated a 400-fold increase in suicide rate among dialysis patients as compared with the normal population.

There are several reasons why depression frequently accompanies medical illness. In some cases, such as Cushing's disease with its high concentration of corticosteroids (82), changes in the central nervous system may be the consequence of the disease itself. In other cases, the medications used to treat the disease have been implicated as depressogenic agents, e.g., antihypertensives (such as reserpine or propranolol), steroids (such as oral contraceptives, cortisol, and corticotropin), sedatives (such as benzodiazepines), as well as other drugs (83). Moreover, depression can result from the stress of coping with a chronic or acute illness, as well as from the losses frequently associated with such illness (64).

We have considered thus far how physical illness (either the disease process itself or its treatment or its psychological consequences) can bring about depression. We now explore how depression in turn tends to exacerbate medical illness. Dirkx et al. (84) introduced the term "psycho-maintenance" for the process in which psychological and behavioral factors tend to maintain and increase the perceived severity and medical intractability of an already-established illness.

Patients with end-stage chronic renal disease provide an illustration. In a retrospective study of 286 home-dialysis patients, Wai et al. (85) found depression and age of the patient to be the only study variables significantly associated with shortened life span. One could postulate that the decrease in motivation and initiative seen commonly in depression must surely have an adverse effect on patients' willingness and ability to comply with exacting medical regimens such as those entailed by hemodialysis. This would then contribute to the progress of the disease itself.

The same may also be true for other chronic diseases such as diabetes mellitus. In a descriptive study of 50 insulin-dependent diabetics, Surridge et al. (86) frequently found increased fatigue, irritability, and depressed mood. Al-
though none of the patients in the sample was suffering from a major affective disorder at the time of the investigation, a quarter of the patients reported depressed mood. Furthermore, higher scores on the Hamilton Psychiatric Rating Scale of Depression (87) were correlated with less careful self-management of the disease (i.e., regularity of seeing physician, adherence to diet, frequency of urine testing, frequency of exercise, and special behavior that could affect metabolism). Lustman et al. (88) also found that patients with major depression and diabetes mellitus had significantly higher HbA1C (a marker for poor glucose control) than patients with diabetes mellitus alone who were not depressed. It is reasonable to suppose that, if mild depression is correlated with poor self-management, then full-blown depression could severely compromise self-care and accelerate the progressive deterioration associated with diabetes mellitus and other illnesses. Thus, it is essential for physicians to monitor the mood states of patients with chronic medical illness as well as the physiological changes induced by that illness.

Treatment Studies of Patients with Depression and Medical Illness

There are three published double-blind placebo-controlled studies of use of tricyclic antidepressants in primary-care outpatients with depression (89–91). Some of the patients in these studies had medical illness and major depression; others had only the affective illness. All three studies demonstrated tricyclic antidepressants to be significantly more effective than placebo. However, subjects in these studies have either been in the more severe spectrum of depressives seen in general practice or the population samples were not well characterized. Moreover, no attempts were made to distinguish characteristics of those who show the drug-placebo differences.

Preliminary results of a recent British study of primary-care outpatients are the first data to appear in this area (92). In this double-blind placebo-controlled six-week trial of amitriptyline vs placebo in a heterogeneous sample of 141 general-practice depressives, particular emphasis was placed on the classification of severity of the affective illness as well as the effect of stress and demographic and historical variables on outcome. Drug was superior to placebo in all groups, except for patients with Research Diagnostic Criteria minor depression and those with lower initial severity (below 13 on the 17-item Hamilton Scale for depression).

There are few treatment studies of patients with both major depression and medical illness, although several promising research studies are currently in progress. In 34 post-stroke patients, nortriptyline was significantly more effective than placebo (93). In 42 medically ill outpatients, trimipramine was statistically superior to placebo (94). A retrospective uncontrolled study of 50 medically ill depressed inpatients treated with various tricyclic antidepressants found that only 40% of the patients responded to treatment and 32% of the tricyclic antidepressant trials were terminated because of side effects (delirium occurred in 16% of these patients) (95). Although this study has several methodological flaws (retrospective design, uncontrolled design, lack of objective ratings for depression), it does point out the need for further placebo-controlled trials in medically ill patients.

Several ongoing studies of patients with major depression and medical illness have reported promising initial results, including: (a) Borson et al. (96), in patients with chronic obstructive lung disease; (b) Craven (97), in patients with end-stage renal disease; and (c) Katon (98), in patients with chronic tinnitus.

Psychological Negotiation

Because many patients with major depression selectively focus on the somatic components of the depressive syndrome, and because depression and a chronic medical illness frequently occur together, the first step in treatment of depression in the medical setting is negotiation of explanatory models with the patient (99). Many patients react to the diagnosis of depression with defensiveness and feel that their physician does not believe they have “real” physical symptoms. It is helpful with these patients to educate them about the biological research on major depression. An explanation that major depression is a syndrome encompassing somatic, affective, and cognitive symptoms and that research has demonstrated that there is a biochemical abnormality in specific catecholamine systems of the brain, often decreases patient defensiveness. In depressed patients with a medical illness such as chronic pain, it is often helpful to describe depression as a frequent secondary reaction to severe pain or medical illness, i.e., a somatopsychic illness. This explanation avoids patient defensiveness about the physician not believing that their pain is the primary problem. Moreover, it is often very difficult to determine which illness began first (e.g., chronic pain or depression), and depression is a frequent secondary reaction to medical illness.

Psychopharmacological Treatment

Tricyclic antidepressants, monoamine oxidase inhibitors, electroshock treatment, and specific types of psychotherapy all have proven efficacy in the treatment of major depression (100). Here, we focus on the tricyclic antidepressants. Table 6 reviews the pharmacological properties of the polycyclic antidepressants.

A useful strategy in using these medications is to utilize their side-effect potentials to treat the major symptoms from which the depressed patient is suffering. Thus the physician might choose a medication with marked sedative action such as doxepin or amitriptyline to treat a depressive with marked agitation and insomnia. On the other hand, the physician might choose an activating medication such as desipramine or protriptyline to treat a depressive with hypersomnia, marked lethargy, and psychomotor retardation. Tricyclics with the greatest alpha1 adrenergic receptor-blocking property are thought to have the greatest ability to reduce psychomotor agitation, while the tricyclics with the most effect on norepinephrine uptake best energize a lethargic patient. There has also been speculation that the relative affinity of these drugs for 5HT2 receptors may be related to their propensity to exert anxiolytic effects (101). All available tricyclics have some degree of anticholinergic action, and the possible clinical side effects include blurred vision, constipation, dry mouth, sinus tachycardia, urinary retention, and memory dysfunction (101). Should a serious anticholinergic side effect occur, the physician could change the medication from one high or moderately high in anticholinergics to one with low anticholinergic effects.

All currently available tricyclic antidepressants significantly affect the heart (102). They tend to slow both atrial and ventricular depolarization, and they cause an increase in PR, QRS, and QT intervals and a decrease in T-wave
amp;#39;The tricyclic antidepressants all have quinidine-like effects on the heart, slowing conduction time through the Bundle of His. Like the other Group I antiarrhythmics, tricyclics can cause abnormally slow post-AV-nodal conduction. Thus it is not surprising that therapy with tricyclics can strikingly decrease ventricular irritability, and so ventricular ectopy is not a contraindication to the use of tricyclics (103). Patients with pre-existing bundle-branch blocks seen on their electrocardiogram are probably the most sensitive to tricyclic cardiac effects and should be treated with the greatest caution: start with very low dosages, 25 mg, and increase very gradually, following the patient with serial electrocardiograms. Whether or not tricyclics decrease myocardial contractility in therapeutic dosages is still controversial. In one recent study (104), radionuclide ventriculography was used to measure ventricular ejection fractions before and during maximum exercise in depressed patients who had heart disease and who were being treated with therapeutic doses of doxepin or imipramine; no adverse effects on left ventricular function were noted. Roose et al. (105) recently found in a group of 21 patients with major depression and left ventricular impairment that ejection fraction was unchanged by nortriptyline.

The second most common side effect of the tricyclic antidepressants is orthostatic hypotension, and clinical experience dictates that this is the most frequent dosage-limiting problem in the successful treatment of depression. Although orthostatic hypotension has been thought to be due to the specific antidepressant's affinity to alpha, adrenergic receptors (Table 6), the relative hypotensive effects of specific drugs do not follow the alpha-receptor-blocking tendencies. Several factors are thought to increase the likelihood of orthostatic hypotension: (a) the presence of cardiovascular disease (106), (b) the presence of a pre-treatment postural systolic blood pressure drop greater than 10 mmHg (107), (c) the concomitant use of one or more drugs that can lower blood pressure (108), and (d) the type of antidepressant medication used (101).

Four studies have reported on the prevalence of significant orthostatic hypotension. In a sample of mostly geriatric depressed patients, many with cardiac dysfunction, 24% of imipramine-treated patients required discontinuation of treatment (109). Three other studies reported clinically significant orthostatic hypotension in 7% to 20% of patients who were being treated with tricyclic antidepressants (107, 108, 110).

Orthostatic hypotension of at least 20 mmHg occurs in 25% of the aged, and it often contributes to the elderly's susceptibility to dizziness and falling (111). Blumenthal and Davie (112) determined that 40% of 100 geriatric psychiatric outpatients complained of dizziness and falling, and 27% had a systolic drop in excess of 20 mmHg. About 40% of this geriatric population were prescribed tricyclics or monoamines, and 27% had a systolic drop in excess of 20 mmHg. Some conditions—such as diabetes, peripheral neuropathy, cardiovascular and cerebrovascular disease, varicose veins, electrolyte imbalance, and idiopathic orthostasis—largely account for the increased prevalence of orthostatic hypotension in this age group (113). Antihypertensive agents, diuretics, tricyclic antidepressants, hypnotics, and monoamine oxidase inhibitors, alone or in combination, are among the most common offending prescription medications.

The following are guidelines to minimize the potential of serious sequela secondary to orthostatic hypotension (113).

- Take baseline orthostatic blood pressure on medically ill and geriatric patients, and evaluate patients thoroughly for the presence of medical conditions predisposing to orthostasis, including idiopathic orthostasis.
- The dosage of nonpsychotrophic agents with a propensity to induce orthostasis should be reduced, when possible, before a second drug is added to the therapeutic regimen.
- Tricyclic antidepressants should be started in very low dosages and increased gradually, while orthostatic changes are monitored. If orthostatic changes occur, dividing the dosage to twice or three times daily is very helpful.
- Whenever possible, blood pressure and pulse should be monitored daily with the patient in the lying and standing positions, especially during the first week of treatment and after dose adjustments upward.
- The patient should be instructed to not rise abruptly after having been in the lying or sitting position for some time.
- Surgical elastic stockings can be prescribed during the first few weeks of treatment to prevent blood pooling in the extremities. Abdominal binders have been reported to be effective in intractable cases, as is the occasional addition of a stimulant (i.e., methylphenidate).
- Use nortriptyline, which may have a decreased potential to cause orthostatic hypotension compared with other tricyclics, in high-risk patients. A recent study found that only 5% of nortriptyline-treated elderly patients with cardiac constrictive disease and congestive heart failure developed
orthostatic hypotension, as compared with 42% of this same patient sample when they were treated with imipramine (105).

Conclusion

Major depression is one of the most common clinical conditions that primary-care physicians diagnose and treat. The evidence suggests that, despite the high prevalence of depression, it is frequently not accurately diagnosed because of the patient’s and primary physician’s preferential focus on somatic complaints. Pain complaints seem especially common in patients with major depression.

There are few double-blind placebo-controlled studies of tricyclic antidepressants in primary-care patients with depression, but virtually all such studies have found tricyclic antidepressants to be superior to placebo. Side effects such as anticholinergic, cardiac, and orthostatic blood-pressure problems are common, and geriatric medically ill patients are especially susceptible to these effects. Orthostatic hypotension, in particular, often is a dosage-limiting problem in medically ill patients, and guidelines to try to minimize this side effect were suggested.

More education, in medical school and in the continuing medical education curriculum, is needed to increase diagnostic accuracy in affective illness. Also, increased education on the tricyclic antidepressants is needed, because these medications are often underprescribed and inadequately dosed.

References
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98. Katon W. Depression, pain and somatization. Ibid.