Underuse of Evidence-Based Pharmacotherapies for Affective Disorders

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In recent decades psychiatry has experienced a rapid expansion in its pharmacopoeia. More medications are now available, many of which are simpler to use and have better side effect profiles than older agents (1–3). In the rush to embrace these newer medications, older but effective agents are being left behind (4–6). However, evidence-based guidelines for unipolar and bipolar affective disorders include recommendations for the use of older agents—such as tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and lithium—as the treatment of choice for certain subsets of patients (7,8). Especially in cases of nonresponse to first-line treatments, use of these agents may be more advantageous than multiple trials of newer ones (4,9).

Here we review the evidence base for the use of tricyclics, MAOIs, and lithium and summarize the barriers to effective use in clinical practice. We also offer suggestions for organizing practice resources to promote the inclusion of these agents in guideline-level care for affective disorders.

Indications for use

MAOIs are clearly indicated in the treatment of atypical and treatment-resistant depression. Both American Psychiatric Association (APA) (10) and British Association for Psychopharmacology (11) guidelines for the treatment of major depressive disorder state that MAOIs are particularly effective for depression with atypical features such as hypersomnolence, hyperphagia, and weight gain. The recommendations were based on a series of clinical trials with more than 400 patients (12–15) and on a comprehensive review of 55 randomized, controlled clinical trials (16). Both sets of guidelines note that MAOIs are effective treatments for patients who have failed previous antidepressants, on the basis of clinical trials that demonstrate MAOIs to be effective for as many as 50 percent of patients resistant to previous drug therapy (17).

Tricyclics have a long track record of efficacy for the treatment of major depression (18). Early studies suggested that they were superior to selective serotonin reuptake inhibitors (SSRIs) for treating severe or melancholic depression (19). However, more recent trials and meta-analyses have shown that both classes are equally effective across depressive subpopulations, with the possible exception of the superiority of tricyclics for depressed psychiatric inpatients (20). Because of their established efficacy in treating neuropathic pain, tricyclics may be the treatment of choice for patients with depressive disorders and comorbid pain (21).

Among patients who fail to respond to treatment with an SSRI, switching out of the SSRI class to a tricyclic antidepressant may be more effective than switching within the SSRI class (a 73 percent response rate compared with a 50 percent response rate) (22). An advantage of the tricyclic nortriptyline is the ability to ensure a therapeutic blood concentration, allowing clinicians to assess adherence and to efficiently move patients to a therapeutic dosage, thus performing a time-limited trial (19). This is not the case with the newer antidepressants, which can lead to protracted trials of increasing dosages.

Medication costs are lower for tricyclic antidepressants and MAOIs than for the newer agents. However, under usual practice conditions, overall costs do not differ between SSRIs and tricyclics; higher medication costs for SSRIs are balanced by lower outpatient visit costs (24).

Since its introduction, lithium has been a mainstay of treatment for bipolar disorder and an effective augmentation strategy for depression (4,5,25). The APA practice guidelines for bipolar disorder recommend lithium as the first-line treatment for classic mania and bipolar depression (8), although augmentation with other medications, such as antipsychotics, may be required for rapid control of acute mania. Lithium remains the only medication that has been approved by the Food and Drug Administration for maintenance treatment of bipolar disorder (4). The Cochrane Collaborative confirmed the efficacy of lithium as maintenance therapy for manic depressive disorder (26) while finding equivocal evidence for divalproex and valproic acid as maintenance treatments (27). Lithium is also the only mood stabilizer that has been shown to reduce the

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risk of suicidal behavior among patients with bipolar disorder (28).

Drug acquisition costs are lower for lithium than for anticonvulsants (29). Some studies have suggested that divalproex is associated with shorter inpatient treatment for mania, a major component of overall costs of care for patients with bipolar disorder (30), although prospective randomized, controlled trials are necessary to establish the overall cost-effectiveness of lithium compared with divalproex.

Lithium augmentation is a first-line treatment for treatment-resistant unipolar depression (25). A key meta-analysis of double-blind, placebo-controlled studies found that treatment-resistant patients were more than three times as likely to respond to lithium as to placebo augmentation (31).

Declining use of older agents

Despite the efficacy of tricyclic antidepressants and lithium, the frequency of prescription of these agents has declined in recent years (6,32), whereas the use of MAOIs declined since concerns about dietary restrictions came to light in the mid-1960s (33). Fluoxetine was introduced in the United States in 1987; by 1993–1994 SSRIs comprised more than half of antidepressants prescribed in the National Ambulatory Medical Care Survey (34). Use of SSRIs among elderly persons increased from 33 percent of all antidepressant prescriptions in 1992 to 77 percent in 1997 (3). Other countries have witnessed similar trends (35).

Of more than 400 psychiatrists surveyed in 2000, 93 percent indicated that SSRIs were their first-line treatment preference (36). Respondents perceived that SSRIs were more effective than tricyclics and MAOIs, even for severe depression. In another provider survey, even when asked to switch medications for patients whose illness was refractory to an adequate trial of an SSRI, most clinicians chose to use newer antidepressants; only 10 percent chose a tricyclic and 1 percent chose an MAOI (37).

According to the National Ambulatory Medical Care Survey, more than half of psychiatric visits for bipolar disorder in 1992–1993 included a prescription for lithium, compared with only 30 percent in 1996–1997 (6). At the same time, there has been a rapid expansion in the number of agents being used to treat bipolar disorder, with a trend toward increasing off-label use of anticonvulsants (4,5). Similarly, despite a strong evidence base for lithium augmentation in unipolar depression, its use for this indication has declined over time in Britain and the United States (25).

Why have older agents with solid evidence bases fallen into relative disuse? Concerns from both patients and physicians about side effects and dietary and medication interactions have likely contributed to low rates of use of MAOIs (33). MAOIs have significant antiadrenergic, anticholinergic, and antihistaminic side effects. Perhaps even more bothersome is the need to restrict ingestion of tyramine-rich foods, sympathomimetic drugs, and certain narcotics because of the possibility of hypertensive crisis. Furthermore, the combination of MAOIs and other serotonergic agents may result in a potentially life-threatening serotonin syndrome. Reversible inhibitors of monoamine A or transdermally administered selegiline, which do not require dietary restrictions, may make MAOIs more appealing if they become available in the United States (33).

Tricyclics also have antiadrenergic, anticholinergic, and antihistaminic properties that may cause them to be less tolerable than SSRIs and other newer agents (24). Of particular concern are the cardiovascular side effects of tricyclic antidepressants and the potential lethality in overdose (38). However, outcome studies suggest that clinical and quality-of-life outcomes are comparable among patients treated with SSRIs and tricyclics (24).

Lithium has come to be viewed by some as a toxic drug that is difficult to use (4,5). It can disrupt thyroid function and lead to renal problems; however, it does not affect the liver or pancreas, as may other mood stabilizers, and thus lacks significant interactions with medications that are hepatically metabolized (4). Lithium can also induce sinus node dysfunction, potentially leading to bradyarrhythmias or syncopal episodes (4). As with other mood stabilizers, it may cause weight gain and exacerbate dermatologic conditions (4).

Use of tricyclics, MAOIs, and lithium may thus require closer monitoring to assess for side effects and toxicity. Patients with cardiac risk factors should receive baseline electrocardiograms before starting tricyclics or lithium (4,38). Thyroid and renal function should be assessed before lithium is started, and drug concentrations should be monitored during therapy (4). However, laboratory assessment is also required before and during therapy with most anticonvulsants shown effective for bipolar disorder. Young psychiatrists may not receive necessary training in starting and monitoring patients on older agents (5).

Finally, the rise in popularity of some of the newer agents may be due to aggressive marketing by pharmaceutical companies to physicians and the general public (5). Older agents whose patents have expired are no longer promoted.

Strategies for increasing use

Admittedly, the older agents may be more difficult to use than newer ones. Nonetheless, these older agents have a crucial role to play in psychopharmacology. MAOIs and tricyclics are important alternatives for certain subpopulations and for patients who do not respond to SSRIs or newer agents (9–11). Lithium remains the standard for the treatment of euphoric mania and bipolar depression and for maintenance treatment of bipolar disorder (7,8). Clinicians, faced with increasingly large caseloads and fewer resources, may need additional supports to effectively make use of these evidence-based medications.

Soon after the introduction of lithium in the United States, lithium clinics were developed that organized care by using integrated teams of psychiatrists and medical paraprofessionals who implemented structured treatment protocols. These included standardized schedules for patient visits and use of symptom rating forms. Because much of the treatment protocols could be carried out by paraprofessionals under the supervision of psychiatrists, evidence-based care could be delivered to large numbers of patients at modest cost. Similar clinic models have been used to ensure the safe and effective use of clozapine.

In primary care settings, the rates

and quality of depression care have also been improved by the use of multifaceted interventions that utilize nonphysicians to support evidence-based care by physicians. A designated care manager—usually a nurse or a social worker—provides patient education, monitors depressive symptoms with use of standardized rating scales, reminds patients of appointments and laboratory tests, assesses for side effects, provides feedback to the prescribing physician, and may provide short-term manualized psychotherapies. In these programs, primary care providers have easy access to evidence-based guidelines and psychiatric consultation. Both care managers and providers use computerized patient registries that track patients' progress and automatically remind providers of necessary follow-up.

Strategies borrowed from these models could be implemented in specialty mental health settings to improve the appropriate use of tricyclics, MAOIs, and lithium. The elements pertinent to supporting use of these agents include evidence-based protocols and active follow-up by clinical support staff. Organized patient education could provide added benefit by motivating patients to monitor symptoms and side effects and adhere to medication regimens and dietary restrictions. For psychiatrists in training, exposure to such systems of care could provide needed skills in the proper use of these medications. ♦

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