Major depression is one of the most challenging illnesses for the medical community. Despite intense efforts in continuing medical education, the disorder remains largely unrecognized by the patient, under-recognized and under-treated by general practitioners and mental health specialists, and a quite resistant condition that is highly recurrent. This may be attributable in part to the erroneous perception that depression is not a medical problem but merely a group of commonly encountered benign and nonspecific symptoms. It is still surprising that we have difficulties convincing many of our colleagues that major depression shares many of the problems and complications of widely recognized “physical” illnesses.

The frequent treatment-resistance and recurrent nature of depression fits well into medical models. For example, if hypertension is left untreated, there will be progressive damage to the vasculature; if depression is allowed to persist, atrophy can occur in brain structures. If an infection is treated only until fever abates, not only will symptoms recur, but antibiotic resistance may develop. Similarly, children with asthma who are kept asymptomatic have a better prognosis into adulthood; a partial antidepressant response will often be followed by a relapse occurring sooner than if the episode had been thoroughly treated.

Therefore, clinical practice in depressive disorders often deviates from guidelines used to manage severe physical illnesses. Combination therapy with a bronchodilator and a corticosteroid for severe asthma is standard practice. However, in severe depression often complicated by uncertainty with regard to suicide, a single agent may be administered at a fixed dose for weeks awaiting a response. Furthermore, prescribing a tricyclic agent can provide the tool with which the patient can complete a suicide gesture. This represents a mismatch between intervention and the acuity/severity of the problem.

In this month’s CNS Spectrums, we present four articles concerning depression and one original report on the occurrence of cavum septi pellucidi in relation to schizophrenia. In the first article, Dr. Lépine and colleagues provide striking statistics from elegant and very large European studies with respect to low rates of consultation in patients with depression, suboptimal performance of healthcare professionals in recognizing the disorder, and inadequate prescribing practices. Although some differences are noted in countries on both sides of the Atlantic, the healthcare-seeking behavior of patients and the overall management of depression are far from what anyone would expect for such a serious and sometimes life-threatening condition. During the study, Lépine and colleagues noted that patients with depression consulted their general practitioner more often, which one would have expected to increase detection. However, the effect appeared to be contradictory. Moreover, controversy still exists with respect to the superior efficacy of tricyclics versus selective serotonin reuptake inhibitors (SSRIs), which may explain in part the relatively high prescription rate for tricyclics. In their study, patients administered SSRIs reported feeling more like their normal selves than those given a tricyclic. This may have a negative influence on compliance with the former first-generation antidepressants and relapse rates. These are only a few examples of the wealth of results amassed from the study’s tremendous data bank.

In this issue’s second feature, Dr. Bremner provides a scholarly overview of the crucial concept that depression may result in significant atrophy of certain brain structures. Studies also indicate that the degree of atrophy is proportional to the duration of the depressive episode. He makes a compelling argument favoring the notion that elevated levels of glucocorticoids can be the main cause for this neuronal degeneration. Furthermore, it appears that some memory functions are directly affected by glucocorticoids. Since these findings have been replicated by more than one group, one cannot help but think that major depression might be considered a neurodegenerative disease. In the aforementioned epidemiologic study, the average time from onset of depression to its diagnosis was nearly 4 years. Aside from the fact that this would categorize patients into a chronic state by most standards, this would also allow significant brain atrophy to occur.

However, all news is not bad. In the next article, Dr. Duman nicely summarizes his groundbreaking work on neurogenesis. Indeed, the notion that neurons in the brain do not regenerate at all is obsolete. In a brain structure implicated for decades in depression and antidepressant response (ie, the hippocampus), nearly 10,000 new cells are born daily. The deleterious effect of glucocorticoids on neurogenesis is also emphasized in this article utilizing evidence generated in various studies. This phenomenon can thus be tentatively linked to well-documented atrophy of at least the hippocampus. In this particular brain region, Dr. Duman has shown that antidepressants can up-regulate a second messenger cascade and enhance the production of brain-derived neurotrophic factor. This substance has the potential to induce neurogenesis not only in the hippocampus, but in other structures as well. Aside from confirming the validity of targets beyond membranal receptors, this pivotal work raises the possibility that depression-induced regional brain atrophy can be reversed by antidepressants.

The first three papers this month establish a need for a greater effectiveness in the treatment of major depression. The fourth article, by Blier and Ward, presents the possibility that the antidepressant response can be accelerated and enhanced, and offers strategies to achieve these goals. After presenting the several advantages and few inconveniences of using aggressive pharmacotherapy for major depression, it is hoped that the case is made for using optimal site-directed approaches, as in other serious medical conditions.