The title of this column is “Psychopharmacology and Psychotherapy” rather than “Psychopharmacology or Psychotherapy.” While many mental health care professionals seem to take an “either/or” approach to these two treatment modalities, I believe that is both wrong and short-sighted. While this column typically focuses exclusively on clinical psychopharmacology, that should not be taken to imply that I believe psychotherapy is unimportant. In fact, I believe potential advances in the treatment of psychiatric illnesses will only be achieved by the complementary use of psychotherapeutic approaches. I also believe that advances in psychopharmacology will enhance patients’ ability to benefit from psychotherapeutic approaches. To illustrate how psychopharmacology and psychotherapy are complementary rather than antagonistic strategies, I often compare the treatment of psychiatric illnesses to computers and orthopedic surgery when speaking to medical students and residents.

A way of categorizing psychiatric illnesses

Table 1 shows a method of grouping neuropsychiatric illnesses into three major categories based on likely differences in underlying pathophysiology.

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
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<tbody>
<tr>
<td>Predominantly hardware</td>
<td>Senile dementia of the Alzheimer’s type</td>
</tr>
<tr>
<td>Predominantly software</td>
<td>Simple phobia</td>
</tr>
<tr>
<td>Combined hardware and software</td>
<td>Panic disorder</td>
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Table 1. The division of neuropsychiatric illnesses into three categories based on likely different pathophysiology

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onset and degree of dementia is well correlated with the extent of hardware problems in the brain (i.e., the amount of neurofibrillary tangles, amyloid plaques, and neuronal loss). Other examples of neuropsychiatric illnesses of the “predominantly hardware” type include Huntington’s chorea, Parkinson’s disease, and the various spongiform dementias.

In simple phobia, on the other hand, there may be no underlying hardware problem. Instead, anyone can probably develop a simple phobia by being exposed to the right environmental setting for the phobic reaction to occur—i.e., the presentation of a novel or near novel stimulus (e.g., a mouse, snake, blood) paired with the emotional reaction of fear or startle (unconditioned response). With either a sufficiently strong one-time exposure or with repeated exposures, the novel stimulus is able to elicit fear, which is now a conditioned response. Admittedly, there may be some stimuli (e.g., heights) for which there is a built-in or hardware predilection for a fear response in the human brain.

The latter caveat reflects the fact that most psychiatric illnesses are likely the result of a complex interaction between hardware and software issues. An example is panic disorder, in which the primary problem in many cases probably involves hardware at the level of the brainstem mechanisms designed to detect suffocation. In this paradigm, the brain mechanisms responsible for sensing and reacting to the condition of suffocation are faulty and detect suffocation when it is not present. Nevertheless, the brain perceives suffocation and reacts accordingly with a sympathetic outflow leading to extreme mental and physical activation designed to enable the organism to escape suffocation. Again, this column is not meant to provide an exhaustive review of the pathophysiology of panic disorder, and some researchers disagree with the suffocation model and would offer alternative theories. Nevertheless, this theory of panic disorder, based on work in the 1970s and 80s by numerous researchers from different disciplines and popularized by Klein,1 is useful as an example of a condition involving both “hardware” and “software” problems. The “suffocation” model proposed for the pathophysiology of panic disorder is analogous to a faulty fire alarm that sends out a false warning leading to the evacuation of a building or home. In this theory of panic disorder, the sufferer pairs an unconditioned response (i.e., a panic attack) with an environmental stimulus such as a crowded environment. Over time, the environmental stimulus (e.g., the crowded environment) alone (without the panic attack) is sufficient to elicit fear and avoidant behavior (i.e., learned responses).

The analogy between computers and psychiatric treatment

The simple system for classifying psychiatric illnesses proposed here suggests that the treatment of psychiatric illnesses can be compared to the management of computer hardware and software problems. From this point of view, somatic approaches to psychiatric illnesses such as clinical psychopharmacology are principally aimed at the hardware level of psychiatric illnesses, whereas psychotherapeutic approaches are principally aimed at the software or learning level. However, this analogy does break down at points. For example, no computer has been created that can rival the ability of the human brain to reshape itself in response to its environment, which is the essence of learning. Thus, new learning, which is arguably the goal of psychotherapy, can change brain “hardware.”2,3

Nevertheless, the software-hardware analogy, while oversimplified, illustrates why taking an either/or approach to psychopharmacology and psychotherapy is not appropriate. It would be as if a computer manufacturer only cared about building the most advanced hardware without any consideration for the fact that the computer needs software to be functional. The same is true for the designer who develops software without considering the capabilities of the computer that must run it. Both approaches are doomed to failure.

When faced with a malfunctioning computer, the first step is deciding whether the problem is one of hardware, software, or their interface—so it is when treating patients with psychiatric illnesses. Imagine the results if a computer engineer approached all computer problems from a hardware-only or software-only approach. Trying to correct a hardware problem with a software solution or the reverse is not going to result in an optimal outcome; nor will it when treating patients with psychiatric illnesses. The goal of building a better computer is to be able to run better software. The same is true for developing better somatic approaches to psychiatric illnesses. From this perspective, the goal of somatic treatment is to address underlying “hardware” problems in the brain so the patient can obtain benefit from psychosocial and psychotherapeutic interventions aimed at installing more functional (i.e., “better”) “software.”

Psychiatry as orthopedics

Another useful analogy involves the similarity between treatment of psychiatric and orthopedic problems. Imagine a patient comes hobbling into an orthopedic
surgeon. The surgeon notes the patient is not bearing weight on the right leg and is not moving the right knee. In response, the surgeon, taking a software-only approach, explains to the patient how the failure to bear weight on the leg and to move the knee will lead to muscular atrophy and joint contracture, respectively. The surgeon therefore advises the patient to go run laps. However, the patient has a broken right leg and running laps will only aggravate the basic problem.

Most readers will object that no competent orthopedic surgeon would take such an approach with a patient. However, this column is about trying to understand where we are now and where we may be in the future. From this perspective, consider that physicians who were once considered competent engaged in treatments that today seem as bizarre as the orthopedic surgeon advising lap running for a broken leg. Examples include the use of blood letting and the rejection of Ignaz Semmelweis’ theory concerning the role of handwashing in preventing hospital-based infections (failure to follow Semmelweis’ admonition is apparently still a major cause of acquired infections in the hospital).

The point of this scenario is that what seems appropriate today may well seem ludicrous tomorrow. The field of psychiatry must be particularly humble in this respect since the brain and human behavior remain the most challenging areas that medicine has to address and much remains to be learned. Recall that only a hundred years ago, some psychiatrists advocated using psycho-analysis as a treatment for patients with dementia.

To put this matter into a clearer temporal perspective, in the article by Gaudiano in this issue (“Is Symptomatic Improvement in Clinical Trials of Cognitive-Behavioral Therapy for Psychosis Clinically Significant?” p. 11), the author states that “...one would not expect most individuals with severe, chronic mental disorders, such as schizophrenia or autism, to return to normal functioning post-treatment.” Taken from today’s perspective, that statement is true, but it will hopefully seem naïve in the future. The goal of treatment research is not only to return the patient to normal functioning but to prevent the illness from developing altogether. There is every reason to believe that that goal will be achieved for schizophrenia in the future, just as investigational treatments that will hopefully prevent SDAT are in clinical trials now, and just as, today, statin drugs prevent or delay the onset of atherosclerotic vascular disease and protease inhibitors prevent or delay the onset of acquired immunodeficiency syndrome (AIDS). A few years ago, those advances would have seemed unfathomable to some. Thus, this column should be interpreted not from the perspective of what we currently believe about how things are but, instead, from the perspective of how they can be in the future.

With this caveat in mind, we return to the scenario of the patient with the broken leg and the orthopedic surgeon. Consider an alternative to the version presented above in which the surgeon takes a hardware-only approach and casts the leg after the X-ray reveals a fracture. Several weeks later, the surgeon removes the cast when a repeat X-ray shows that fusion has taken place and sends the patient on his way with the pronouncement that he is healed. Although this scenario probably seems more realistic to many readers, the surgeon in this case has nevertheless failed to take into account the muscular atrophy and joint contracture that may have developed during the time needed for fusion to occur — and hence the need for physical therapy to help the patient achieve maximum functional restoration of the injured leg. In fact, the fall that resulted in the fracture may itself have been due to poor conditioning of the leg and/or instability of the joint which could have been corrected by physical therapy, thus preventing the fall.

The treatment of psychiatric illnesses is analogous in that the first step is determining whether the primary problem is at the level of hardware, software, or the combination, while the second step involves applying the correct interventions in the correct sequence to achieve maximal functioning of the organ (i.e., the brain in the case of psychiatry).

Why synapses?

Figure 1 shows the traditional illustration of the presynaptic neuron and the postsynaptic neuron separated by a gap, the synapse. The brain can be likened to a computer that is designed to operate at the speed of electricity, with axons insulated by myelin to allow for rapid conduction of nerve impulses. Yet, this rapid signal transduction is slowed to the level of a chemical messenger being propelled across a synapse.

Why is the signal transduction slowed in this way or, in other words, why have synapses? One answer is that synapses are not hardwired, but instead are malleable or capable of being changed. That re-modeling of the brain, the process we call learning, involves complex changes, including gene activation and protein synthesis, in groups of neurons. Such learning can occur at the level of motor function, can involve signal recognition such as sensory processing, or can encompass more complex levels of neural functioning such as abstract thought. Psychotherapy is directed at the ability to learn new...
responses rather than being dependent solely on hardwired responses. Psychopharmacology and other somatic treatments can correct hardware issues that prevent the ready acquisition of new learning and thus can facilitate psychotherapy. In fact, it is probable that the use of some clinical somatic advances will only be practical when combined with psychotherapeutic approaches.

It is obvious from this discussion that psychopharmacology and psychotherapy are complementary. In the end, both are mediated by their ability to facilitate remodeling of the brain. As noted earlier, this fact is where the hardware-software dichotomy of the computer analogy breaks down, since software in the brain becomes hardware, and hardware problems in the brain may prevent appropriate software from being assimilated. Nevertheless, I have found this analogy a useful initial step in understanding the complex interplay between psychopharmacology and psychotherapy and helpful in moving away from the “either/or” approach that has been taken by too many in the field over the years.

Will drugs to treat residual symptoms of schizophrenia ever be practical without being combined with psychotherapy?

This question, and the whole issue discussed here, came home to me when I was testing a novel antipsychotic a few years ago. The drug had been rationally designed to affect only one receptor subtype of a neurotransmitter. This specific receptor had been hypothesized to be specifically involved in the pathophysiology of schizophrenia based on a number of basic science studies.

The gene coding for this receptor had been isolated, its amino acid sequence characterized, and the three-dimensional configuration of the receptor itself deduced. Using this information, structure-activity relationships had been constructed and molecules developed to stereoselectively fit that receptor and no other. In vivo imaging studies using positron emission tomography and specific radioligands had been conducted, showing what dose of the new drug was needed to occupy 95% of the receptor in human beings. Phase I studies had demonstrated that such a dose could be given to a normal human being with good safety and tolerability. We were now prepared to do a bridging study between phase I and phase II.

A bridging study is in essence a test of the drug in a population of participants who have, but are not acutely ill with, the illness the drug was developed to target. Such studies thus provide a bridge between investigations in normal volunteers and phase II acute efficacy trials. (For more background on drug development, readers are referred to an earlier series of columns by the author.)

In this study, the participants were middle-aged males who predominantly had residual symptoms of schizophrenia, that is, mainly deficit symptoms (i.e., asocial, amotivational, and anhedonic symptoms), with minimal, if any, positive symptoms (i.e., hallucinations, delusions, and thought disorder). In most, if not all, of the participants, their illness had begun in the early to mid-teens.

The study started out uneventfully. However, after about 2 weeks, I received reports from the nursing staff that the drug was making the participants worse. In contrast, I had thought the participants were doing better. What was the difference in our observations and what was the drug really doing?

The participants were becoming more talkative, more active, and more interested in their surroundings. Their increased interest included noticing that most of our nursing staff were females while they were males. They had begun to express interest in the nursing staff; however, they had all of the social skills of early adolescent boys. In other words, it was as if the drug had taken them back to the stage in psychosocial development when they should have learned how to approach the opposite sex.

Although to me the drug showed great potential as a treatment for deficit symptoms, its development was discontinued. Why? My impression was that the company saw no way to develop the drug without requiring that it be used with a psychosocial rehabilitation program. Imagine the potential consequences of dispensing such a drug to outpatients with this illness without such a program. I believe this represents a case of a drug not being developed because of the inability to use it except in combination with a psychotherapeutic approach.
**Conclusion**

This column will hopefully provide a useful and complementary juxtaposition to the article by Gaudiano in this issue (p. 11). In that article, the author correctly points out that, despite current pharmacotherapy, many individuals with schizophrenia experience residual symptoms and poor quality of life and also that early attempts at psychotherapy for individuals with this illness often either showed no efficacy or made the condition worse. For this reason, Gaudiano reviewed the literature on more modern attempts at psychotherapy for individuals with psychosis who have had an incomplete response to current pharmacotherapy. The point of this column is that the latest advances in antipsychotic psychopharmacology have been at best an incremental, rather than an innovative, improvement. Truly innovative improvements will depend on fundamental discoveries about the pathophysiologies and pathoetiologies of the illnesses that are now lumped together under the term schizophrenia. Until future innovative somatic treatments are capable of preventing the illness, somatic treatments aimed at restoring normal function will by necessity require the concomitant use of psychotherapy to accomplish that goal. As we develop a better understanding of the functional anatomy of the brain at both the systems and molecular level, I suspect that we will be faced with more challenges such as the one described above, so that innovative, investigational somatic treatments will either require or significantly benefit from being combined with psychosocial rehabilitation to demonstrate their true efficacious potential. Consider the treatment of panic disorder as a model for a combined approach being used today. Medications can be directed at correcting the faulty brain mechanisms but they cannot, in and of themselves, correct the conditioned responses to environmental stimuli, the avoidant behavior, and the low self-esteem and interpersonal problems that typically occur in patients with panic disorder. That is why I believe an either/or approach to treatment is likely doomed to fail whether considered from the perspective of the drug developer or the practicing clinician, whereas combined treatment is most often both complementary and necessary for the maximum benefit of the patient.

The analogies used in this column, like all analogies, have limitations but I have found them useful in helping medical students, residents, physicians in practice, and even patients and families understand this treatment model and how hardware and software interventions in psychiatry are necessary and are not unlike their counterparts in other fields of medicine and science. The major limitation of these analogies is related to the complexity of the organ that we treat, the brain. Unlike today’s manmade computers, the brain is a living computer whose purpose is to integrate the functioning of different bodily systems and respond to its environment—it is this ability to respond to the environment that blurs the distinction between what we call hardware and software. In the human brain, software becomes hardware, and at the same time, hardware can prevent or hamper acquisition of optimal software. Despite the limitations of the analogy, the concepts of hardware and software have heuristic value for conceptualizing and using combinations of psychopharmacology and psychotherapy for the benefit of our patients. Psychiatrists and other mental health care professionals can benefit from taking a page out of computer sciences and orthopedic surgery when treating patients with psychiatric illnesses, in particular chronic and recurrent disorders. The goal is optimal restoration of the patient’s functional capacity to the level achievable with today’s treatments used to their fullest potential. That requires addressing both hardware and software issues and doing so in the proper sequence.

**References**