Fewer classes of drugs for more and more psychiatric disorders

L. Trevor Young, MD, PhD

Department of Psychiatry, University of Toronto, Toronto, Ont.

Psychopharmacology has a critical place in defining biological psychiatry. In fact, psychiatry may be unique among the fields of medicine in that many of the theories of the pathophysiology of major mental illnesses are based on the putative mechanisms of action of agents used to treat these disorders. For example, the monoaminergic theory of mood disorders was largely based on the actions of reserpine with its well-documented effects in potentiating the release of monoamines[1] — a theory refined and supported by the introduction of monoamine oxidase inhibitors and tricyclic antidepressants. Similarly, the dopaminergic theory of schizophrenia was largely founded on the mechanism of action of neuroleptics with regard to their effects on dopamine neurotransmission and, later, dopamine receptors.[2] On the other hand, bipolar disorder has defied biochemical characterization, perhaps in part due to the unique and diverse agents used to treat the different phases of this illness.

Pharmacologically defined biological psychiatry has stood us in good stead in many respects and has allowed us to focus on a relatively small number of theories. Furthermore, psychopharmacological agents are useful tools in experiments in biological psychiatry. Indeed, the diligent work of many committed scientists has provided our field with volumes of data on many of these drugs, which have been applied to a whole host of psychiatric illnesses. Since the early days of psychopharmacology, some 5 decades ago, we have seen an explosion of new antidepressants, antipsychotics, anticonvulsants and novel pharmaceutical agents. While this has the potential to further expand and validate models of major mental illness, one fact suggests that we might need to change our thinking, that is, the remarkable efficacy of single agents in many psychiatric illnesses, and even in opposite symptoms — as in the case of mania and depression both responding to the same drug.[3]

The effectiveness of selective serotonin reuptake inhibitors (SSRIs) was initially demonstrated in depression, then very rapidly in anxiety disorders, obsessive–compulsive disorder (OCD), substance dependence, as well as other illnesses,[4] and more recently in the negative symptoms of schizophrenia.[5] The atypical antipsychotics are even more remarkable in the breadth of their effects, which have been demonstrated in states ranging from the acute positive symptoms of schizophrenia to the negative and residual cognitive impairment in that disorder,[6] and in the treatment and prevention of relapse of acute mania in bipolar disorder.[3] This class of drugs is also commonly used to induce or promote sleep,[7] is very popular in treating agitation in the elderly,[8] and may reduce anxiety and improve symptoms of OCD at low doses as adjunctive agents to SSRIs,[9] although some drugs in the class such as clozapine have been reported to exacerbate OCD symptoms when given at higher doses.[10] In addition, atypical antipsychotics have been shown to augment the effect of antidepressants in major depression[11] and have antidepressant effects as monotherapies, at least in bipolar disorder.[3] This latter finding is particularly interesting, because mania and depression are often thought to be biochemical opposites.

The broad therapeutic profiles of these medications challenge some of the traditional tenets of biological psychiatry. However, there are many examples in psychiatry where compelling theories and models are not based on the psychopharmacology of specific agents such as antidepressants or antipsychotics. For example, setting aside the monoaminergic theories of bipolar disorder allowed for recent important developments in better understanding the pathophysiology of this disorder. In this regard, whereas the robust effects of lithium on a number of signal transduction pathways provide an example of the old model of elucidating the pathophysiology of the illness based on drug targets, the unexpected findings of cell loss and damage,[12] and more recently of mitochondrial dysfunction and energy metabolism,[13] in bipolar disorder allow us to appreciate the underlying mechanisms of this illness unrelated to the effects of this drug on neuronal receptors and components of signal transduction pathways. There are indeed a series of findings demonstrating very robust neuroprotective effects of lithium in animal models.[14] Although these effects have

Correspondence to: Dr. L. Trevor Young, Centre for Addiction and Mental Health, 250 College St., Toronto ON M5T 1R8; fax 416 260-4189; trevor_young@camh.net

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only been suggested using brain imaging in patients with bipolar disorder,[15] there is no reason to presume that lithium would not have the same effect in patients as demonstrated in animal studies. More important, there is virtually no evidence linking these neuroprotective properties to the effects of lithium or other mood stabilizers on the signs and symptoms of the illness (i.e., the antimanic, antidepressant or prophylactic activities of these drugs). This suggests that the pathophysiology of bipolar disorder is much more complex than the pharmacological treatment of the illness originally indicated.

In another example, the work of Swedo and colleagues suggests that damage to the basal ganglia after childhood exposure to *Streptococcus* A may result not only in a movement disorder, but also in the signs and symptoms of OCD in later childhood or early adulthood.[16] This suggests a model of illness novel to psychiatry with both a specific cause, an infectious agent, and a specific affected brain region, the basal ganglia.

A final example is the neurodevelopmental model of schizophrenia. Whereas elegant work still continues on the dopaminergic theory of schizophrenia (and a Nobel prize awarded for much of the work associated with this model), other researchers have turned their attention toward birth factors, childhood and the prodrome of the illness.[17] From this latter work, a very compelling model of aberrant brain development and altered neural connectivity has emerged that may go a long way toward improving our understanding of this chronic illness. Importantly, atypical antipsychotics are being evaluated in this illness not just based on their acute effects in the treatment of psychosis, but also to determine whether they are effective in preventing or slowing the onset of schizophrenia once prodromal symptoms occur.[18]

It is time for us to take a similar approach to understanding psychiatric disease to that in internal medicine, pediatrics and pathology. Like our colleagues in these fields, we could start to revisit whether psychiatric illnesses are caused by one or more of the usual list of suspects: infection, inflammation, neoplasm, ischemia or inborn errors of metabolism, to name a few. This might give us a fresh perspective and understanding of the mechanisms of the illnesses we treat and, ultimately, a broader range of treatment options than we now possess. The explosion in psychopharmacology has given us what many have described as "psychotropics," a class of agents with a broad spectrum of efficacy that provides us with many well-tolerated alternatives for a wide variety of illnesses. However, and perhaps more important, it also frees us from the limitations of the psychopharmacologically influenced understanding of the pathophysiology of major mental illness.

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