Chapter 1

History of CNS drug development

Sheldon Preskorn

Introduction

The intent of this chapter is to provide a conceptual framework for the rest of the book from both a historical and a forward-looking perspective.

Like all of medicine, drug development in psychiatry began with a series of chance discoveries from the 1930s to the 1960s. These drugs in large measure validated the following psychiatric syndromes: manic-depressive illness or bipolar (affective) disorder (i.e., lithium), unipolar affective disorder or major depression (i.e., iproniazid and imipramine), schizophrenia (i.e., chlorpromazine), and anxiety disorder (i.e., barbiturates, then meprobamate, and subsequently diazepam). Those initial drugs began the re-medicalization of psychiatry and served as probes into brain function which provided a means of better understanding the mechanisms underlying their clinical effects and thus the potential pathophysiology underlying these psychiatric syndromes (Goodwin and Preskorn, 1982; Preskorn, 1990).

Those drugs also permitted the development of technology (e.g., specific receptor binding) that permitted the rational development of newer drugs starting in the late 1960s and early 1970s and continuing to the current day. However, the rational development of psychiatric drugs in the 1970s and 1980s was generally limited to improving upon the pharmacology of the chance discovery drugs rather than developing truly novel medications. That was due to the limited understanding of the biology under both psychiatric and neurological diseases.

From the period of the 1980s to the current day, three other and inter-related developments occurred: (a) the industrialization of drug development process, (b) the dependency of major pharmaceutical companies ("big pharma") on the "blockbuster" (i.e., drugs that could generate one billion or more dollars in revenue per year) business model, and (c) the adoption of a commodity (e.g., soap) style marketing and sales approach (e.g., "new and improved Tide"). Until recently, block busters have generally been drugs which treated large percentages of the population (i.e., common diseases) chronically. That in turn means that the drug must be safe, well tolerated and effective for a large number of people and not just in one country but throughout the world, which in turn means not being susceptible to adverse interactions with the increased biological variance inherent in the world population.

The dependency on blockbuster drugs in turn has led to the industrialization of the drug development process and an emphasis on speed (to save patent life and thus maximize potential revenue, i.e., a month delay could translate into a loss of $100 million in

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revenue for a drug capable of generating $1.2 billion a year revenue). Following the adage that haste makes waste, the urgency to shorten the drug development process has set the stage for both the increase in the placebo response and the increased failure rate of drug development programs.

CNS drug development is at a critical fork in the road: (a) the promise of an increased ability to develop truly novel drugs and to better target those drugs for specific subsets of the populations and (b) the implosion of the blockbuster business model. The latter has led to the recent decision by two major pharmaceutical companies to stop developing drugs for psychiatric indications.

This chapter will cover these big picture topics by principally focusing on drug development for psychiatric as opposed to other central nervous system (CNS) indications such as neurological conditions, pain, and sleep. That decision was made to keep the chapter within the length guidelines established for it. Nevertheless, the principles outlined in this chapter are generally applicable to the development of drugs for these other indications. In addition, specific comments will be made about drugs for senile dementia of the Alzheimer's type, which, like a number of other neuropsychiatric conditions, falls outside the division between psychiatry and neurology.

Early drugs

Before discussing specific new early CNS drugs, the following is important from a historical perspective: the modern era of clinical psychopharmacology owes its beginnings to antibiotics, beginning with Fleming's discovery of penicillin in the 1920s and further enhanced by World War II (Geddes, 2008; Demain and Sanchez, 2009; Ligon, 2004). Fleming accidentally dropped crumbs of moldy bread into Petri dishes in which he was growing bacteria over a weekend. When he returned, he found that bacterial growth had been prevented in the areas of the Petri dishes where the bread crumbs had fallen. He concluded that there must be an antibacterial factor in the mold. He therefore set out to isolate that factor, which he subsequently called penicillin. World War II provided the incentive and the financial backing to develop methods for mass production of penicillin to treat infections secondary to combat trauma (Keefer, 1970; Richards, 1964). That was the basis for launching the pharmaceutical industry that exists today.

The contribution of antibiotic pharmacology to modern clinical pharmacology goes further: once an effective antibiotic was isolated from a plant (i.e., mold), organic (or medicinal) chemists could begin modifying the structure to develop new variations which (a) were patentable, (b) were capable of being reliably synthesized in commercial quantities, and (c) had some demonstrable and hence commercial advantage such as improved efficacy, safety, tolerability, or ease of administration when compared to an older antibiotic. This same approach became the universal approach in all therapeutic areas including CNS medications.

Table 1 lists the first drugs in psychiatry and the decade they were initially discovered.

These early drugs were principally discovered in two ways. The first was by observing the medicinal effects of plants. That approach dates back to before written history. The second occurred with the evolution of organic chemistry, permitting first the isolation and characterization of the active ingredients in plants (e.g., penicillin) and followed by the

Table 1. The early CNS drugs, class, and decade of discovery for a CNS indication

Drug	Class	Decade of discovery
Amphetamine	stimulant	1880s AD (Google, 2010)
Cocaine	analgesic/stimulant	1830s AD (Google, 2010)
Chlorpromazine	antipsychotic	1950s AD (Lopez-Munoz *et al.*, 2005)
Diazepam	anti-anxiety	1950s AD (http://itech.dickinson.edu/chemistry/?p=497, 2008)
Imipramine	antidepressant	1950s AD (Maxwell and Eckhardt, 2009)
Isocarboxazid	antidepressant	1950s AD (Darling *et al.*, 1959)
Lithium	mood stabilizer	1940s AD (Prien *et al.*, 1971)
Morphine	analgesic	2100 BC (Norn *et al.*, 2005)
Phenobarbital	anticonvulsant	1930s AD (Brink, 2010)
Reserpine	antipsychotic	1950s AD (Stitzel, 1976; Preskorn, 2007)

synthesis of new molecular entities which could then be manufactured in large quantities. Morphine and reserpine are examples of the former while chlorpromazine and imipramine are examples of the latter.

From chance to science: from chlorpromazine to newer antipsychotics and antidepressants

Chlorpromazine was a discovery which had its origins in the German aniline dye industry of the late 1800s and early 1990s (Lopez-Munoz *et al.*, 2005). Chlorpromazine and other phenothiazine molecules were synthesized around the turn of the last century and some were initially used to treat pinworm infestation. However, chlorpromazine over the last 50 years has come to play a pivotal role in the modern era of clinical psychopharmacology. This modern era began in large measure with Henri-Marie Laborit, M.D., a French surgeon, who recognized the calming effects that chlorpromazine exerted in anxious French patients going to surgery. Based on that observation, Dr. Laborit encouraged his French psychiatric colleagues to use it in French patients with anxiety disorders. They in turn found that chlorpromazine did have anti-anxiety effects at low dose (i.e., what they termed minor tranquilizing effects) and so they also tried it in agitated psychotic individuals. To their amazement, chlorpromazine at higher dose not only calmed agitated psychotic patients but actually reduced their psychotic symptoms (i.e., what they termed major tranquilizing effects). That observation ushered in the modern era of antipsychotic medications.

Soon after this discovery, chemists began working to tweak the phenothiazine structure of chlorpromazine to produce new drugs. Through such work, they produced other "low potency" antipsychotics such as thioridazine and clozapine (synthesized in 1960) and high potency phenothiazines such as trifluoroperazine and fluphenazine. They also produced derivatives which were, to their chagrin, inactive as antipsychotics

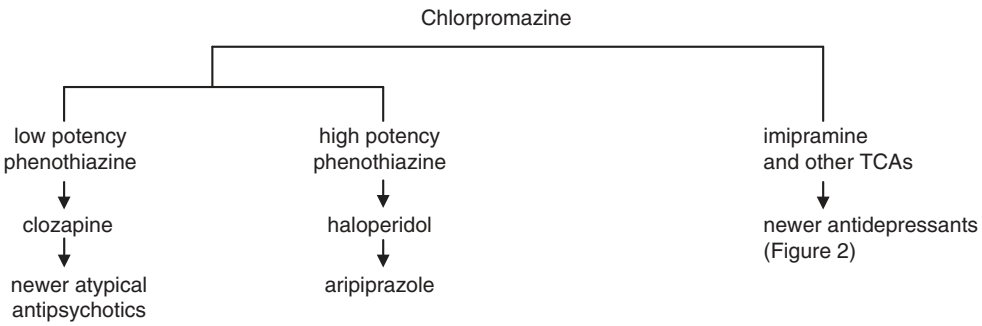

Figure 1. From chlorpromazine to conventional and atypical antipsychotics and TCAs.

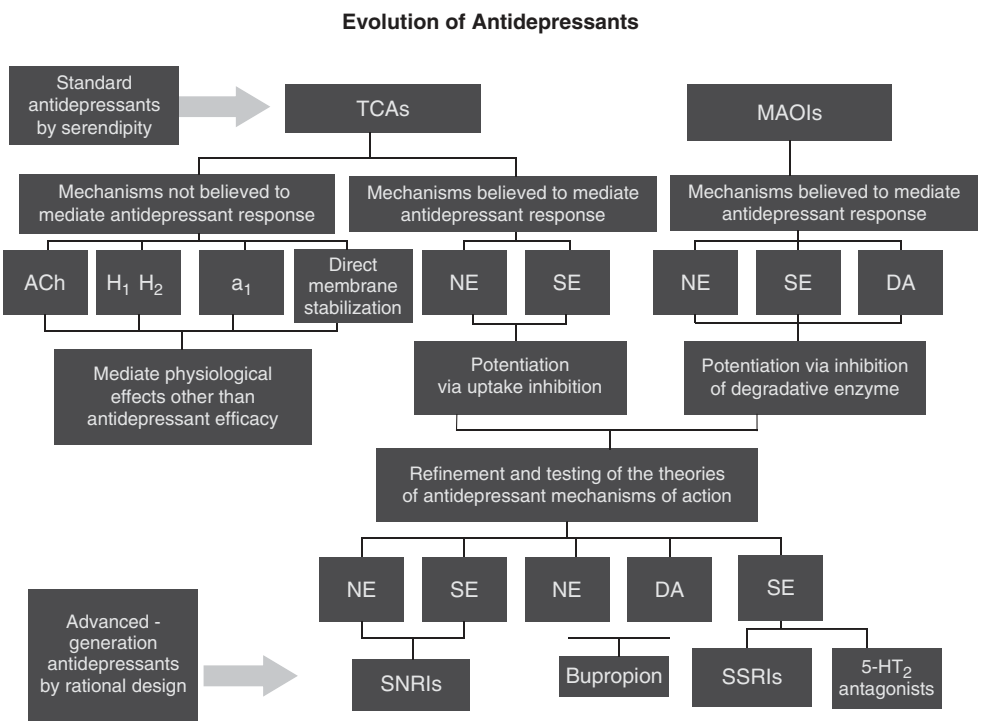

Figure 2. From TCAs and MAOIs to newer antidepressants. See plate section for color version.

but to their surprise, active as antidepressants (e.g., imipramine). Thus, chlorpromazine gave birth to atypical and conventional antipsychotics and to tricyclic antidepressants (TCAs) (Figure 1). As discussed below, TCAs together with monoamine oxidase inhibitors gave birth to all of the other newer antidepressants we have today including serotonin selective reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) (Figure 2) (Lopez-Munoz and Alamo, 2009; Moncrieff, 2008; Preskorn, 1996).

Parenthetically, due to commodity marketing and sales, psychiatrists now widely believe that there are two generations of antipsychotic medications: conventional and

atypical (Weiden *et al.*, 2007). They further believe that atypical antipsychotics are a new development. In fact, chlorpromazine – the first generally successful antipsychotic – and most of the other low potency phenothiazines meet most of the criteria as atypical antipsychotics (Preskorn, 2001) (Table 1). So "atypicality" is not new but old. The advertisements for thioridazine in the 1960s and 1970s are hardly distinguishable from the advertisements for newer antipsychotics. In fact, the advertising "war" in that era was between thioridazine and haloperidol, which was the new drug on the block touting its selective effects only on dopamine (D)-2 receptors without all of the other effects of thioridazine. Thus, there are actually four generations of antipsychotics: (a) the early atypicals such as chlorpromazine, thioridazine, and clozapine, (b) the selective D-2 pure antagonists (e.g., haloperidol), (c) the newer atypicals, and (d) the partial D-2 agonist (e.g., aripiprazole). What are now referred to as conventional antipsychotics means selective D-2 antagonists and does not properly include the low potency phenothiazines. The adjective "low potency" refers to the fact that these drugs have lower binding affinity for D-2 receptors than they do for other receptors. An unintended consequence of the commodity marketing seen as necessary to achieve blockbuster status is that the credibility of the pharmaceutical industry has fallen (i.e., commodity marketing and sales require that the drug must be new and improved even if the claims are only partially correct). That would have only affected physicians were it not for direct to consumer advertising, which has changed the image of big pharma from an enterprise aimed at improving the human condition to one akin to soap and automobile companies (i.e., selling product) (Huh *et al.*, 2010).

The era of the 1960s: understanding basic CNS pharmacology and developing early animal models of CNS diseases

The late 1950s and particularly the decade of the 1960s was a period of rapid growth in the understanding of biogenic amine (i.e., dopamine (D), norepinephrine (NE) and serotonin (5-HT)) transmitter systems in the brain, with Jules Alexrod and others leading the charge. During this period, the CNS anatomy of the biogenic amine neurotransmitter systems was mapped. The enzymatic pathways for their synthesis and degradation were elucidated as well as the mechanisms mediating their release, their reuptake and their pre- and post-synaptic receptors. That was accomplished in large part by studying the CNS pharmacology of the early CNS drugs (Table 1). Jules Axelrod received a Nobel Prize in 1970 for the work conducted in his lab on these issues (http://nobelprize.org/nobel_prizes/medicine/laureates/1970/axelrod-bio.html, 1972).

Scientists used the pharmacology of these early drugs to develop the initial theories of the pathophysiology of psychotic and depressive disorders (i.e., the hyper-dopamine theory of schizophrenia and the deficiency of biogenic amine theory of major depression) (Tost *et al.*, 2010). They also used the effects of these drugs to produce the first animal models of psychiatric illness, such as the dopamine hyperactivity model produced in a variety of ways such as intoxicating rats and other rodents with amphetamines to produce species-specific stereotypic movements. This was used to screen for D-2 selective antagonists such as haloperidol, which for 20 years during the decades of the 1970s and 1980s dominated the treatment of patients with schizophrenia and other psychotic disorders (Ayd, 1980; Demuth and Ackerman, 1983). In an analogous way, reserpine, tetrabenzapine

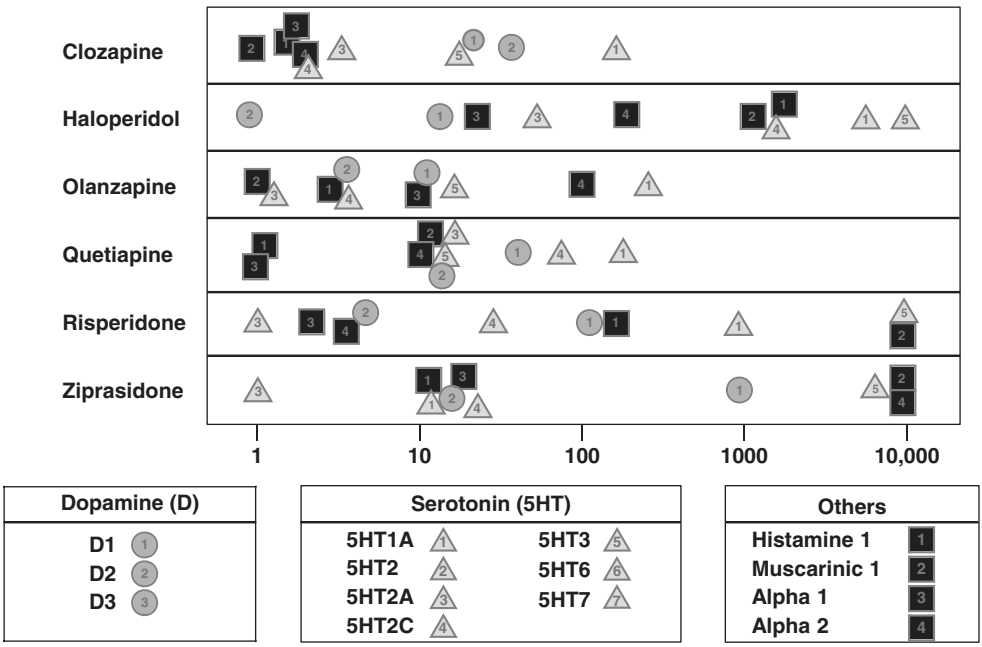

Figure 3. Comparison of the binding affinity of chlorpromazine, haloperidol and newer "atypical" antipsychotics. The profile for each drug is expressed relative to its most potent binding. See plate section for color version.

and various neurotoxic derivatives of amphetamine (e.g., para-chloramphetamine) were used to deplete the rodent brain of one or more of the biogenic amine neurotransmitters to serve as an animal model of depressive illness in humans.

Another important development in this period was the ability to isolate specific neurotransmitter receptors in test tubes by brain fractionation (Iversen *et al.*, 1975). Via the development of this technology, scientists could begin to study the structure-activity relationship that allowed a drug to have high affinity for one receptor and low affinity for another. That work set the stage for the next era in the modern clinical psychopharmacology: the 1970s and 1980s.

The era of the 1970s and 1980s: redesigning drugs based on receptor pharmacology

Using receptor binding affinity, drug development scientists in the pharmaceutical industry produced new molecular entities using the theories and the techniques developed in the 1950s and 1960s. They either added binding affinities to specific proteins in the case of antipsychotic drugs or reduced them in the case of antidepressants to produce new molecules capable of being patented and simultaneously having truly desirable effects over existing drugs which could be touted by the marketing and sales departments of big pharma.

That was done by establishing the structure-activity relationship needed to mimic some but not all of the effects of the chance discovery drugs. In the case of the newer atypical antipsychotics, the goal was to produce molecules with higher binding affinity

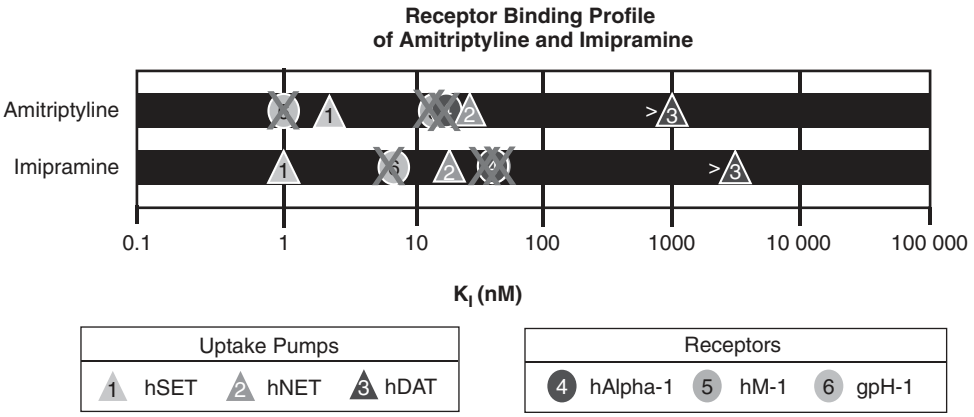

Figure 4. Receptor binding profile of TCAs. See plate section for color version.

for the 5-HT 2A receptor versus the D-2 receptor and minimally or no effects of early low potency phenothiazine on histamine-1 (H-1), muscarinic-1 acetylcholine (M-1), and alpha-1 norepinephrine (alpha-1) receptors (Preskorn, 2009b; Seeman, 2002) (Figure 3). The blockade of those three receptors caused the following generally unwanted effects: sedation and weight gain, peripheral and central anticholinergic effects, and orthostatic hypotension, respectively. In the case of antidepressants, the goal was also to simplify the pharmacology of the TCAs, principally by eliminating their effects on fast sodium channels which mediated their dose-dependent and serious cardiotoxicity and also eliminating their high binding affinity for the H-1, M-1, and alpha-1 receptors (Preskorn, 1996; Preskorn and Irwin, 1982) (Figure 4). As with the early low potency phenothiazines, blockade of those three receptors caused considerable tolerability problems for patients on TCAs. Given that they were analogs of low potency phenothiazines, TCAs not surprisingly shared some of the same pharmacology. In essence, the SSRIs and – even more so – the SNRIs were the TCAs without their limitations, as illustrated in Figure 5.

The major advance of the SSRIs and SNRIs was the fact that they were essentially not lethal when taken in an overdose whereas TCAs were for the prior 25 years the leading cause of death resulting from overdoses in many countries. The reason is that patients treated with antidepressants are prone to attempt suicide and one way is to take an overdose of your medications. Due to the narrow gap between their ability to inhibit the SE and NE uptake pumps versus the fast sodium channels, even a modest overdose of a TCA could be lethal.

While the tweaking of the receptor binding profile of the SSRIs, SNRIs, and the newer atypical antipsychotics did improve the tolerability and safety of these new medications compared to their forerunners, it did not change the mechanisms of action that mediated their desired clinical effects. That is consistent with the fact that the response and remission rates with the newer drugs are not better than those of the older medications and the substantial overlap in their efficacy, given that only a small portion of patients who do not respond to SSRIs will respond when switched to either SNRIs or TCAs (Preskorn, 2009a).

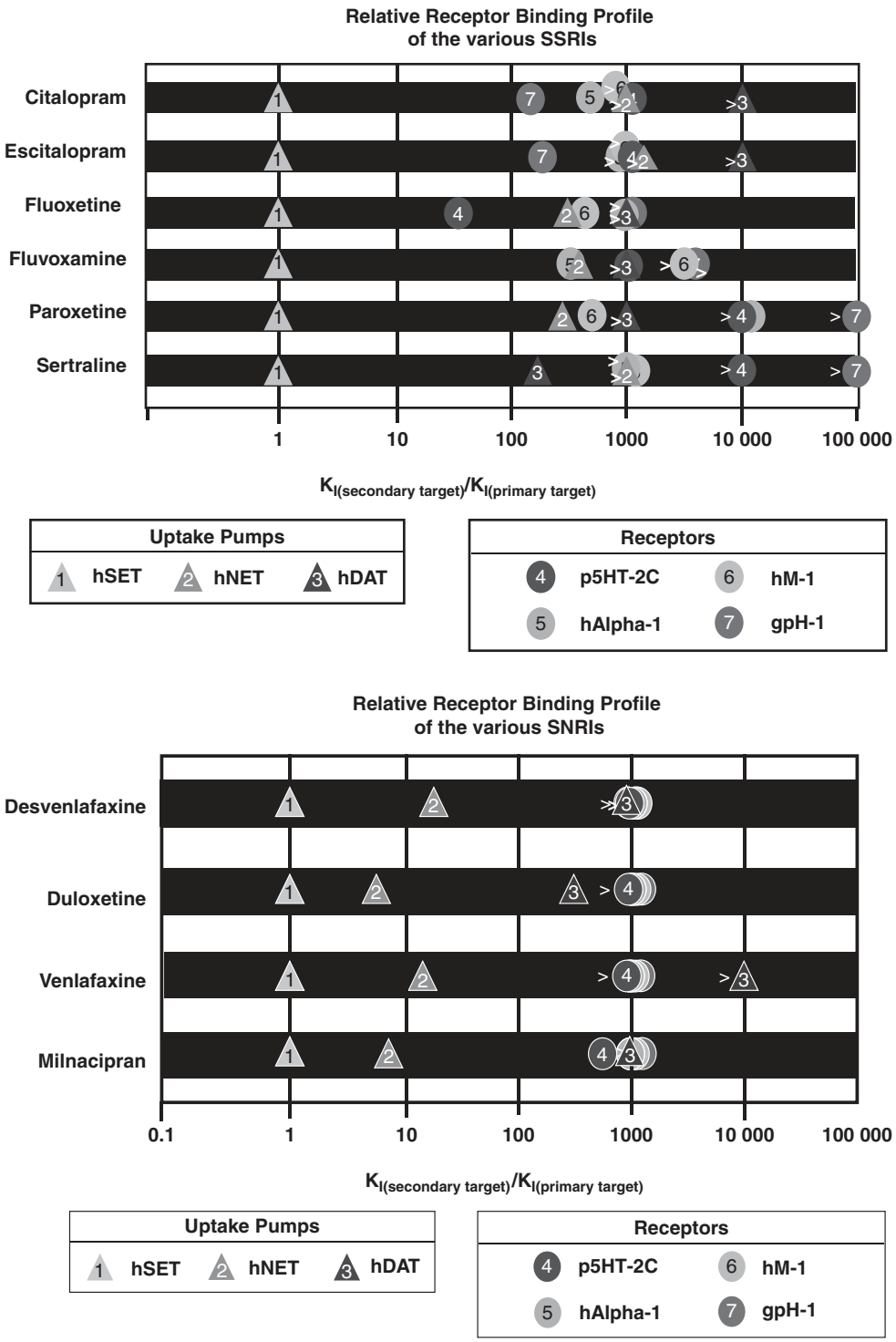

Figure 5. Comparison of the relative receptor binding profile of SSRIs and SNRIs. See plate section for color version.

The human genome project and its implications

The need now is to develop truly novel CNS drugs which work by new mechanisms of action. The hope here is with the human genome project and improved understanding of the molecular biology underlying psychiatric and neurological illnesses. The future can be seen in the dramatic advances being made in medicine for various forms of cancer (Kaelin, 1999; Lai, 2006).

However, there are multiple problems to be solved. The first is that the human genome project has a multitude of potential novel targets for drug development without enough information to know which ones are likely to be the most fruitful for drug development. It has been said that the major effect of the human genome project to date has been to increase the "burn rate" of pharmaceutical companies.

This problem is further amplified by the fact that the blockbuster model may no longer be viable (i.e., one drug to treat a large segment of the population) (Gilbert *et al.*, 2003; www.egonzehnder.com/global/download/issue1bigpharma.pdf, 2008). The reason is that improved knowledge of the molecular biology underlying psychiatric and neurological illnesses may result in splintering what appear now to be one common syndromic illness (e.g., major depression) into multiple better defined illnesses when understood from the level of pathophysiology or pathoetiology. That outcome has occurred in oncology but the approach has been to simply charge more money for the newer drugs to recoup the investment in drug development and turn a profit for the shareholder. The question is whether the same recoup of investment can be made in the case of psychiatric and neurological illnesses given that patients with these illnesses often cannot effectively advocate for themselves and have to rely on others to do that for them.

Two additional contributors to the current dilemma in drug development for psychiatric and neurological conditions are: (a) the cost of drug development due to regulatory hurdles and (b) the industrialization of the drug development process which has occurred over the last 20 years partially in response to the aforementioned cost. The Western world, particularly perhaps the USA, is risk averse. Hence, regulatory agencies (e.g., the Food and Drug Administration in the USA) have been established to protect society from having unsafe drugs on the market. The problem is that medicines with powerful effects on illnesses are likely to produce adverse effects in some individuals as a result of the same mechanisms that produce benefit. That problem is further aggravated by not knowing which people may be at risk for such adverse effects because of either genetic variations, concomitant diseases, or being on other medications. The other problem is that errors of commission (i.e., approving a drug later found to be unsafe in some patients) are more easily detected and likely to be punished than are errors of omission (i.e., discouraging the development of new drugs for serious conditions by making development too costly and too speculative). That can be seen today in the lack of the development of new antibiotics and we are likely seeing the same phenomenon in the decision by companies such as AstraZeneca and GlaxoSmithKline to abandon the development of new psychiatric medications.

The higher hurdle posed by increased expectations for drug development (i.e., number of patients tested and the types of studies done (e.g., thorough QTc studies)) creates two inter-related problems: (a) the process costs more in terms of both money and time and (b) the longer time-line leads to less time left to obtain a return on investment if the drug gets approved.

Industrialization of clinical trials was one solution that pharma developed to address the time-line problem. However, it has now become part of the problem. In this case industrialization refers to several common components of the current drug development process as follows: rigid time-lines for moving drugs from preclinical pharmacology to Phase I and then into Phase II and III; extensive boiler plate inclusion and exclusion criteria which severely limit the number of patients who can enter clinical trials; and the development of clinical trial sites as specialized, for-profit service providers to industry. This approach developed in the 1980s and 1990s when industry was developing drugs which were refinements of already existing drugs (as discussed above) rather than novel drugs with novel mechanisms of action. While there were good reasons for this industrialization in that era, this approach may not work well in the new era when there is greater uncertainty about what to pursue and how to do it.

During the 1980s and 1990s and into the early 2000s, CNS drug development was principally focused on SSRIs, SNRIs, "atypical" antipsychotics, and cholinesterase inhibitors. The SSRIs and SNRIs were derivates of tricyclic antidepressants. The "atypical" antipsychotics were derivates of clozapine. The cholinesterase inhibitors pursued the pathway blazed by tacrine. The endpoints and the time course for the trials were based on what was known from their predecessors. The question now is whether the paradigms and constructs established for drugs which principally affect different forms of biogenic amine neurotransmission are applicable to drugs that may work in fundamentally different ways.

As more about the biology of psychiatric illnesses becomes known, there may be a profound change in the way psychiatric illnesses are understood and codified. Current syndromes may be merged and subdivided in ways distinctly different from the current nomenclature. Treatments may be focused less on symptomatic relief and more on prevention. Such developments would make the current way of developing CNS drugs as antiquated as the buggy whip with the emergence of the gasoline engine.

This book then may be at the beginning of an era when the way CNS drugs are developed may need to be re-thought. If so, that will require flexibility and inherently involves uncertainty, which in turn means risk.

Development of drugs for Alzheimer's disease: a possible model for the future

The current development of drugs for Alzheimer's and other neurodegenerative diseases could be a model for how future CNS drug development might proceed (Becker and Greig, 2008; Bradford, 2002; Chico *et al.*, 2009; Cummings, 2008; Markou *et al.*, 2009; Pritchard, 2008; Steinmetz and Spack, 2009). The current treatments (e.g., donepezil) are symptomatic only and do not alter the course of the illness.

However, several theories about the underlying pathogenesis of Alzheimer's disease have been developed. These theories are based on histopathology, biochemistry, and molecular biology. Over 100 years ago, the microscopic pathology of the illness was known: amyloid plaques, neurofibrillary tangles, and the atrophy and eventual death of neurons. These lesions have now been subjected to biochemical analysis to identify their constituent parts (e.g., beta amyloid 1–42).

From a molecular biology standpoint, there are autosomal dominant forms of Alzheimer's disease. While these cases account for only approximately 1% of Alzheimer's cases, understanding the genetic basis of these cases has the potential to shed light on the