Advances in Neurobiology 30

Matthew Macaluso
Sheldon H. Preskorn
Richard C. Shelton *Editors*

Drug Development in Psychiatry

Springer

Advances in Neurobiology

Volume 30

Series Editor
Arne Schousboe
Department of Drug Design & Pharmacology
University of Copenhagen
Copenhagen, Denmark

Advances in Neurobiology covers basic research in neurobiology and neurochemistry. It provides in-depth, book-length treatment of some of the most important topics in neuroscience including molecular and pharmacological aspects. The main audiences of the series are basic science researchers and graduate students as well as clinicians including neuroscientists (neurobiologists and neurochemists) and neurologists. *Advances in Neurobiology* is indexed in PubMed, Google Scholar, and the Thompson Reuters Book Citation Index.

Matthew Macaluso
Sheldon H. Preskorn • Richard C. Shelton
Editors

Drug Development in Psychiatry

Springer

Editors
Matthew Macaluso
Department of Psychiatry and Behavioral Neurobiology
University of Alabama at Birmingham
Heersink School of Medicine
Birmingham, AL, USA

Sheldon H. Preskorn
Department of Psychiatry and Behavioral Science
Kansas University School of Medicine-Wichita campus
Wichita, KS, USA

Richard C. Shelton
Department of Psychiatry and Behavioral Neurobiology
University of Alabama at Birmingham
Heersink School of Medicine
Birmingham, AL, USA

ISSN 2190-5215 ISSN 2190-5223 (electronic)
Advances in Neurobiology
ISBN 978-3-031-21053-2 ISBN 978-3-031-21054-9 (eBook)
https://doi.org/10.1007/978-3-031-21054-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

About the Editors

Matthew Macaluso is the Bee McWane Reid Professor and Vice Chair for Clinical Affairs in the Department of Psychiatry and Behavioral Neurobiology as well as the Clinical Director of the UAB Depression and Suicide Center. His research focus is on clinical psychopharmacology and its translation to clinical practice with a focus on treatment-resistant major depression.

As clinical director, Dr. Macaluso oversees clinical trials of novel mechanism of action drugs, devices, and biologics to treat patients with severe forms of depression that are not responsive to currently marketed treatments. He is a highly experienced investigator in complex clinical trials and the translational neuroscience of mood disorders and has contributed most significantly in the area of novel treatment development.

Dr. Macaluso completed medical school at the University of Medicine and Dentistry of New Jersey in Stratford, NJ, and graduated from the psychiatry residency program at the University of Kansas School of Medicine, where he was on faculty for 11 years before joining UAB in 2020.

Sheldon H. Preskorn is generally considered one of the world's foremost experts in psychiatric drug development research having worked with over 145 pharmaceutical, biotechnology, devices, and diagnostic companies around the work and was a principal site investigator in all antidepressants and antipsychotics marketed in a 25-year period.

His overarching goal has been throughout his career to bring science to the practice of psychiatry. His research focus is on clinical psychopharmacology and its translation to clinical practice with a focus on otherwise treatment-resistant psychiatric illnesses.

In addition to being a consultant broadly to companies bringing products to the market, he has also worked with the FDA in many different capacities.

Dr. Preskorn did his basic medical training at the University of Kansas School of Medicine where he also completed a two-year residency in anatomical pathology with a focus on neuropathology. He did his psychiatric residency at Washington

University School of Medicine in St. Louis MO. During his residency, he did seminal work on the role of the locus coeruleus in the brain. He has continued related work throughout his more than 40-year career in academic medicine.

Richard C. Shelton is the Charles Byron Ireland Professor and Co-director of the UAB Depression and Suicide Center in the Department of Psychiatry and Behavioral Neurobiology in the Heersink School of Medicine at the University of Alabama at Birmingham. He is an internationally recognized researcher in the areas of translational neuroscience and clinical psychopharmacology of mood disorders.

Dr. Shelton founded and co-directs the UAB Depression and Suicide Center with Dr. Yogesh Dwivedi. The Center has a clinic that provides advanced treatment options for depression including esketamine, electroconvulsive therapy, and vagal nerve stimulation, and it also conducts research ranging from basic molecular neuroscience and genomics to clinical applied research in mood disorders and suicide. Dr. Shelton is a translational neuroscientist, and his work spans from molecules to clinical trials. Recent work has included research on genomic predictors of depression and suicide and advanced therapies for depression.

Dr. Shelton graduated from the University of Louisville School of Medicine and graduated from the psychiatry residency program at the Massachusetts Mental Health Center (now part of the Brigham and Women's residency program) of Harvard Medical School in Boston. He then was a research fellow in the intramural program of the National Institute of Mental Health. He was a professor in the Department of Psychiatry at Vanderbilt University School of Medicine for 26 years before joining UAB in 2012.

Chapter 1
Drug Development in Psychiatry: The Long and Winding Road from Chance Discovery to Rational Development

Sheldon H. Preskorn

Abstract Based extensively on tables and figures, this chapter reviews drug development in psychiatry with an emphasis on antidepressants from the 1950s to the present and then looks forward to the future. It begins with the chance discovery drugs and then moves to through their rational refinement using structure activity relationships to narrow the pharmacological actions of the drugs to those mediating their antidepressant effects and eliminating the effects on targets that mediate adverse effects. This approach yielded newer antidepressants which compared to older antidepressants are safer and better tolerated but nevertheless do still not treat the approximately 40% of patients with major depression (MD) which is unresponsive to biogenic amine mechanisms of action. This form of MD is commonly referred to as treatment resistant depression. Esketamine is an antidepressant which has a novel mechanism of action: blockade of the glutamate NMDA receptor. These studies coupled with earlier studies with other NMDA drugs suggest approximately 60% of patient with TRD are rapidly and robustly responsive to this mechanism of action. Thus, there appears to be three forms of MD based on pharmacological responsiveness: (a) 60% responsive to biogenic amine mechanisms of action, (b) 24% (i.e., 40 × 60%) responsive to NMDA but not to biogenic amine mechanisms of action, and (c) 16% (i.e., 40–24%) not responsive to either of these mechanisms of action. Scientific investigation of these three groups may yield important information about the pathophysiology and/or pathoetiology of these different forms of MD. This information coupled with studies into the neurobiology (e.g., imaging studies, connectomes to name a few approaches being used) and genetics of MD should provide the fundamental knowledge which will permit a rational search for and discovery of newer antidepressant drugs and other somatic and psychotherapeutic approaches to the treatment of patients with different forms of MD based on pathophysiology and

S. H. Preskorn (✉)
Department of Psychiatry and Behavioral Science, Kansas University School of Medicine-Wichita Campus, Wichita, KS, USA
e-mail: spreskorn@kumc.edu

M. Macaluso et al. (eds.), *Drug Development in Psychiatry*, Advances in Neurobiology 30,
https://doi.org/10.1007/978-3-031-21054-9_1

pathoetiology. Examples are given of how such discovery and development have occurred in other areas of medicine and even in central nervous system (CNS) space including six novel mechanisms of action CNS drugs which have been successfully developed and marketed over the last 25 years.

Keywords Antidepressants · Central nervous system biogenic amines · Drug development · Esketamine · Major depression · Mechanism(s) of action · Psychiatric diagnosis · Relative receptor binding · Structure-activity relationships

> [For] knowledge of mental diseases one must have: (a) knowledge of the physical changes in the cerebral cortex, and (b) [knowledge of] the mental symptoms associated with them.
>
> Until this is known, we cannot hope to understand the relationship between symptoms of disease and the physical processes underlying them.—Emil Kraepelin [1], Father of modern psychiatry
>
> Symptoms and behaviors are the output of brain function whereas syndromes are man-made constructions.—Sheldon Preskorn [8]

This Chapter, which was adapted with permission from the Springer Nature book, *Antidepressants: From Biogenic Amines to New Mechanisms of Action*, will discuss the history of antidepressant drug development and put it into the broader context of psychiatric drug development. This chapter will focus on the history of and current status of antidepressant drug development but will also incorporate other concepts relevant to future antidepressants and other central nervous system (CNS) drug development. It will be heavily dependent on the writings of the author on these topics over the last 30 years. The chapter will be primarily focused on illustrative figures and tables with the minimum amount of text needed to explain the figures and tables, put them in context, and then transition to the next topic. All the articles in which figures and tables originally appeared are cited in the reference list. The reader who wants additional text and references on a given topic can do so by referring to the specific cited article of interest.

1.1 Current Status of Psychiatric Diagnosis as a Rate-Limiting Step in Rational Psychiatric Drug Development

In all of medicine, there are four levels of increasing sophistication of diagnosis as illustrated in Fig. 1.1 [12].

The first level is symptomatic diagnosis which is generally the presenting complaint of the patient to the treatment provider. For patients suffering from major depressive disorder (MDD), that presenting complaint may be feeling tired, absence of enjoyment, insomnia, or even headache to name but a few.

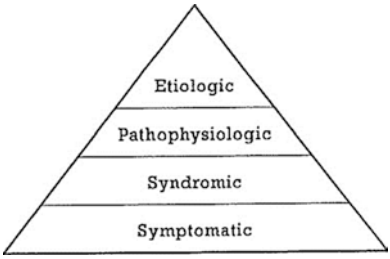

Fig. 1.1 Diagnostic criteria pyramid – the four levels of increasing diagnostic sophistication. (Reproduced with permission from Preskorn and Baker [12]. © Preskorn, 2002)

In general, the psychiatrist is then taught to advance to a second level of diagnostic sophistication which is the syndromic level. The result may be that the patient presenting with these initial complaints may meet criteria for major depressive disorder or perhaps acquired immunodeficiency disorder (AIDS) if the patient also has Kaposi's sarcoma, an opportunistic infection, and generalized wasting.

To reach the third level of diagnostic sophistication illustrated in Fig. 1.1 requires testing for pathophysiological findings. In the case of AIDS, that would be a lowering of the CD 4 count or a positive Western blot test or a high HIV titer. In the case of MDD, there is no generally established testing, but some practitioners might test for cortisol nonsuppression or REM latency which have both been proposed as biochemical test for "endogenous major depression."

To reach the fourth level of diagnostic sophistication illustrated in Fig. 1.1 requires the establishment of a test for the etiological agent or a neurobiological condition which is not established for most psychiatric disorders with the possible exception being testing for the presence of autoantibodies against the NMDA receptor for patients suffering from NMDA receptor-mediated neuroencephalitis. In the case of AIDS, it would be to test for the presence of the etiological agent, the HIV virus.

The above illustrates the basic problem with psychiatric drug development: The field is currently principally stuck at the syndromic diagnosis and has not been able – in general – to advance to the pathophysiological or to the even higher etiological level. However, that is not completely true. In the early 1900s, approximately 20% of admission to psychiatric hospitalization no longer exist. Those conditions were pellagra and general paresis of the insane. The former was due to vitamin D deficiency and the latter to tertiary syphilis. Once those etiological causes were identified and specific treatments identified, those conditions essentially no longer exist in the modern age and instead are consigned to being historical footnotes. In the future, the same will likely be true for major depressive disorder and other similar currently syndromic psychiatric diagnoses.

1.2 What Possible Changes Lie Ahead for Psychiatric Diagnoses?

Considering the philosophy expressed in my quote at the beginning of this paper, the National Institute of Mental Health (NIMH) in 2008 began to develop for research purposes new ways of classifying mental disorders based on behavioral dimensions and neurobiological measures. The goal being to move from the relatively primitive level of syndromic diagnoses to the next level pathophysiological diagnoses (Fig. 1.1).

The author proposed a similar approach in a paper published 34 years earlier and illustrated in Fig. 1.2 [3]. The concept expressed in this figure is that there may be both syndromes which have an underlying biology and dimensional aspects of traits such as impulsivity, IQ, and introversion to extroversion which are independently, biologically, and environmentally determined which can modify the expression of the syndromic cluster such as agitated versus psychomotor retard MDD. Treatments addressing the pathophysiology or even better – perhaps – the pathoetiology of the syndromic diagnosis (MDD) and the pathophysiology of the modifying dimension (e.g., impulsivity) might be the ideal way to approach a given patient.

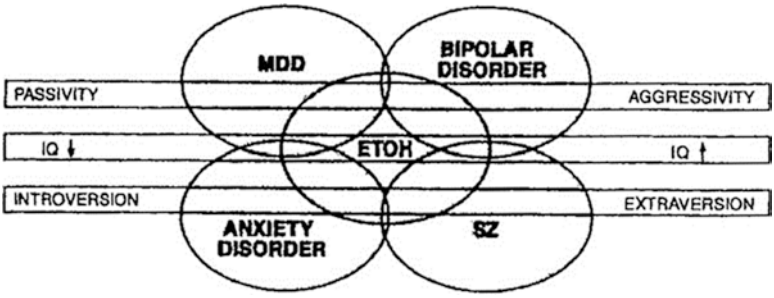

Fig. 1.2 Future of psychopharmacology. Interaction among syndromic diagnoses and between such diagnoses and dimensional aspects of personality. Space and the constraints of being a two-dimensional drawing of three-dimensional phenomena place limitations on this figure. In a three-dimensional figure, it would be clear that there is the potential for overlap between any two syndromic diagnoses and that the syndromic diagnoses are not on a personality trait continuum with respect to each other but rather that such traits are dimensionally present in all diagnoses and influence their expression. This figure also is not meant to imply that there are only three personality traits nor that the three depicted here are necessarily the most important (MDD major depressive disorders, ETOH alcoholism, SZ schizophrenia). (Reproduced with permission from Preskorn [3]. © Preskorn 1990)

1.3 The History of Current Psychiatric Drug Development: Chance Discovery and Rationale Refinement

The current treatment armamentarium for major depressive disorder (and psychotic disorders for that matter) owes their existence to two factors: first, chance discovery and then rationale refinement (Table 1.1) [4–6]. That is particularly true for the treatments aimed at the two of the most major syndromic diagnoses: affective and psychotic disorders.

Chlorpromazine can be viewed as the "Adam" or "Eve" (whichever the reader prefers) to both the family of modern antipsychotics and modern antidepressants as illustrated in Fig. 1.3 [4–6]. In the interest of space and because the themes are the same, this text will not cover the antipsychotic line of the family of drugs while acknowledging that the first widely used class of antidepressants [i.e., tricyclic antidepressants (TCAs)] resulted from a failed medicinal chemistry attempts to develop better antipsychotics. The interested reader can review the primary papers cited in the reference list for details on the antipsychotic lineage if they wish.

Briefly, chlorpromazine begat imipramine as a failed attempt by relatively blind medicinal chemistry to develop a better antipsychotic. The structural change leads to the loss of antipsychotic efficacy (i.e., no to weak D-2 receptor blockade) but the emergence of antidepressant efficacy (due to most likely the ability to inhibit the neuronal uptake of either norepinephrine or serotonin uptake).

About the same time, there was a failed attempt to develop better antitubercular drugs based on the structure of isoniazid produced effective antidepressants. These drugs are called monoamine oxidase inhibitors (i.e., MAOIs) because they presumably work via their ability to inhibit monoamine oxidase, the rate-limiting enzyme in the degradation of three biogenic amine neurotransmitters: dopamine (DA), epinephrine (E), norepinephrine (NE), and serotonin (SE). The antidepressant activity of the MAOIs coupled with the antidepressant efficacy of the TCAs reinforced the

Table 1.1 Early drugs that targeted the central nervous system

Drug	Class	Decade of discovery
Amphetamine	Stimulant	1880s
Cocaine	Analgesic/stimulant	1850s
Chlorpromazine	Antipsychotic	1950s
Diazepam	Anti-anxiety	1950s
Imipramine	Antidepressant	1950s
Isocarboxazid	Antidepressant	1950s
Lithium	Mood stabilizer	1940s
Morphine	Analgesic	2100 BC
Phenobarbital	Anticonvulsant	1930s
Reserpine	Antipsychotic	1950s

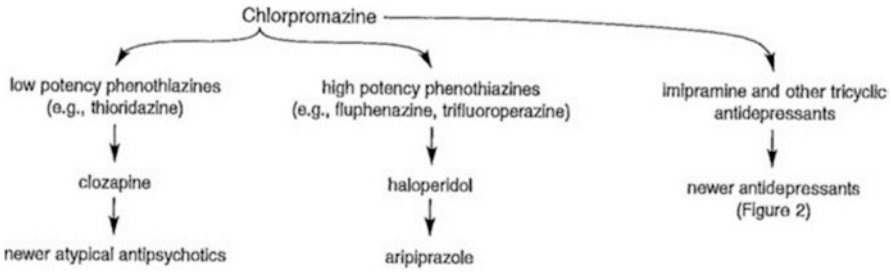

Fig. 1.3 Drug development based on chlorpromazine. (Reproduced with permission from Preskorn [5]. © Preskorn 2010)

idea that deficiency in either SE or NE neurotransmission was responsible for the depressive symptoms seen in patients with MDD.

Armed with the knowledge of the antidepressant activity of TCAs and MAOIs in the 1970s coupled with the ability to use structure-activity relationships and in vitro methods to examine in vitro receptor binding lead to the development via medicinal chemistry of new compounds which were capable of blocking either SE or NE transporters either selectively or in a sequential manner to develop molecules (i.e., 10 times more potent at one than the other or both sequentially over less than a ten-fold concentration range). The former were SE or NE selective reuptake inhibitors, whereas the latter were combined SE and NE reuptake inhibitors over their dosing range (i.e., generally capable of blocking SE reuptake at low concentrations and NE uptake inhibition at higher concentrations) (Fig. 1.4) [4–6]. In the case of bupropion, the goal was to develop a molecule capable of blocking NE and dopamine (DA) reuptake pumps, but the concept is otherwise the same.

The "pharmacological refinement approach" allowed the development of drugs capable of affecting the desirable target (e.g., the SE transporter) at concentrations low enough to not engage from other targets which produce undesirable effects (e.g., acetylcholine muscarinic receptors). Importantly, this approach meant that the new drug did not have a novel mechanism of action different from the earlier antidepressants but instead had a more limited range of pharmacologic actions making it more focused and with a more limited adverse effect profile by eliminating effects on targets capable of mediating adverse effects which were off target.

This strategy has led to the development of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) which are the latest, generally accepted antidepressants.

The consequence of this iterative step without knowledge of the fundamental biology underlying the disorder has led to a plethora of drugs capable of treating patient suffering from a form of the illness which is responsive to their mechanism of action. Table 1.2 shows the relative receptor binding of most currently marketed antidepressants relative to the receptors currently known to be clinically relevant in terms of either producing antidepressant efficacy or "off-target" adverse effects [11].

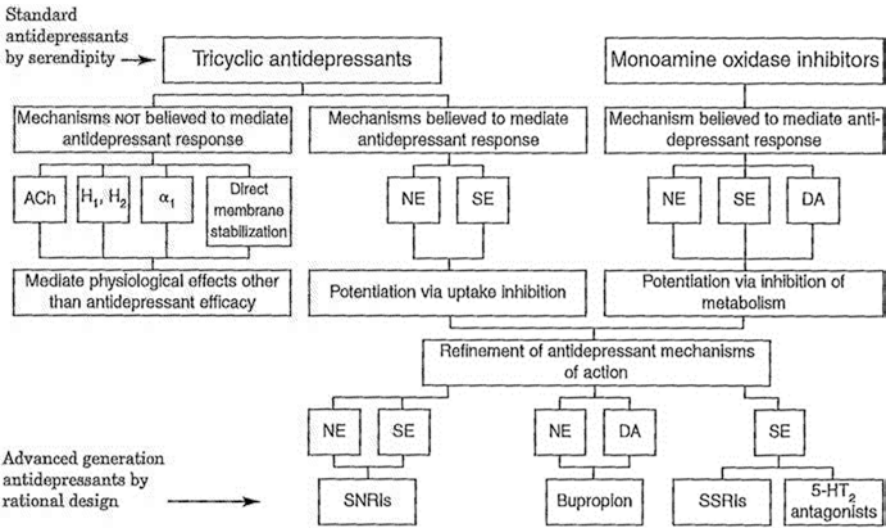

Fig. 1.4 Evolution of antidepressants. ACh acetylcholine, H histamine, α_1 alpha adrenergic, NE norepinephrine, SE serotonin, DA dopamine, SNRI serotonin-norepinephrine reuptake inhibitor, SSRI selective serotonin reuptake inhibitor. (Reproduced with permission from Preskorn [4]. © Preskorn 1996)

All the drugs shown in Table 1.3 [9] are essentially a "rehash" or a realignment of the mechanisms previously suggested to play a role in producing an antidepressant response. The question is: Do they offer anything which is meaning- fully new in terms of additional efficacy? In general, the answer is no based on the results of the largest sequential trial of currently marketed antidepressants ever funded by the NIMH, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D). That study showed that perhaps 40% of patients with MDD have a form of the illness which is not responsive to multiple trials of antidepressants which work via effects on biogenic amine antidepressants (i.e., SE, NE, or DA).

That finding is the reason for the interest in antidepressants which work via non-biogenic amine antidepressants such as ketamine and related drugs.

1.4 The Future or Where to Go from Here?

On the downside, one could look at the last 50 years of psychiatric drug development particularly regarding antidepressants and antipsychotics as an era in which the same mechanisms were rehashed repeatedly. That is simply because these mechanisms were known to work, and not enough was known about the biology of the illness to take many chances on speculative targets. Admittedly, some development work was tried on speculative targets but failed which is the reason why it is

Table 1.2 Antidepressants' relative receptor binding affinity[a]

Generic name	Branded name	hSET	hNET	hDAT	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{2A}
Serotonin and norepinephrine reuptake inhibitors and antagonists at various neuroreceptors and ion channels								
Amitriptyline	Elavil	4	34	>1000				
Imipramine	Tofranil	1	26	>5000				
Nortriptyline	Pamelor	4	1	261				
Selective serotonin reuptake inhibitors								
Citalopram	Celexa	1	>1000	>10,000				
Escitalopram	Lexapro	1	>1000	>10,000				
Fluoxetine	Prozac	1	545	>1000				
Fluvoxamine	Luvox	1	620	>1000				
Paroxetine	Paxil	1	450	>1000				
Sertraline	Zoloft	1	>1000	220				
Selective norepinephrine reuptake inhibitors								
Desipramine[b]	Norpramin	21	1	>1000				
Reboxetine	Vestra	8	1	>1000				
Dual serotonin and norepinephrine (SE ≥ NE) reuptake inhibitors								
Desvenlafaxine	Pristiq	1	27	>1000				
Duloxetine	Cymbalta	1	7.5	504				
Levomilnacipran	Fetzima	1	8	>1000				
Milnacipran	Savella	1	8	>1000				
Venlafaxine	Effexor	1	16	>10,000				
5-HT_{2A} antagonist and weak serotonin reuptake inhibitors								
Flibanserin	Addyi				1	>1000	>1000	49
Nefazodone	Serzone	9	18	17				1
Trazodone	Oleptro	21	>1000	929				1
Specific histamine, serotonin, and norepinephrine receptor antagonist								
Mirtazapine	Remeron	>100,000	>10,000	>100,000				
Dopamine and norepinephrine (weak) reuptake inhibitor								
Bupropion	Wellbutrin	17	95	1				
SSRIs + specific SE receptor activity								
Vilazodone	Viibryd	1	>500	370	21			
Vortioxetine	Brintellix	1	71	>1000	9	33	21	

Table 1.2 (continued)

Generic name	p5-HT_{2C}	5-HT_3	5-HT_7	h alpha1	hM_1	gpH_1	D3	D4
Serotonin and norepinephrine reuptake inhibitors and antagonists at various neuroreceptors and ion channels								
Amitriptyline	–			25	16	1		
Imipramine	–			65	65	8		
Nortriptyline	–			148	34	1		
Selective serotonin reuptake inhibitors								
Citalopram	>1000			757	894	179		
Escitalopram	>1000			>1000	>1000	257		
Fluoxetine	65			>1000	638	>1000		
Fluvoxamine	>1000			560	>5000	>5000		
Paroxetine	>10,000			>10,000	720	>100,000		
Sertraline	>10,000			>1000	>1000	>100,000		
Selective norepinephrine reuptake inhibitors								
Desipramine[b]	–			156	235	132		
Reboxetine	875			>1000	933	44		
Dual serotonin and norepinephrine (SE ≥ NE) reuptake inhibitors								
Desvenlafaxine	>1000			>1000	>1000	>1000		
Duloxetine	>1000			>1000	>1000	>1000		
Levomilnacipran								
Milnacipran	917			>1000	>1000	>1000		
Venlafaxine	>1000			>1000	>1000	>1000		
5-HT_{2A} antagonist and weak serotonin reuptake inhibitors								
Flibanserin		>10,000	990				>100	>10,000
Nefazodone	–			1.2	522	1		
Trazodone	1			5	>1000	45		
Specific histamine, serotonin, and norepinephrine receptor antagonist								
Mirtazapine	–			>1000	>1000	1		
Dopamine and norepinephrine (weak) reuptake inhibitor								
Bupropion	–			10	95	10		
SSRIs + specific SE receptor activity								
Vilazodone								
Vortioxetine		2	12					

Reproduced with permission from Preskorn [10]. © Preskorn 2017

Table 1.2 (continued)
Key: *h* human, *SET* serotonin transporter, *NET* norepinephrine transporter, *DAT* dopamine transporter, *p* porcine, *5-HT* serotonin, *gp* guinea pig, *H* histamine, *M* muscarinic, *D* dopamine, *SE* serotonin, *NE* norepinephrine, *SSRIs* selective serotonin reuptake inhibitors
[a]Relative binding affinity (RRB) is the binding affinity of the drug for every receptor reported in the package insert in relationship to the drug's highest affinity site. To calculate the relative binding affinity for each drug, its *Ki* for its highest affinity site is divided by itself, yielding 1, and next the *Ki* for the highest affinity site (which is the smallest concentration of drug needed to bind to any site) is divided into all its Ki's for lower affinity sites (which is hence a higher concentration needed to bind to a lower affinity site); the result then is a number greater than 1. The larger that number, the higher the concentration needed to bind to the next potential target for the drug
[b]This drug is also a selective norepinephrine reuptake inhibitor
For each drug in this table, its highest affinity and its affinity expressed in nanomolar concentration are as follows: amitriptyline, H_1 (1); bupropion, DAT (526); citalopram, SET (1.6); desipramine, NET (0.83); desvenlafaxine, SET (115); duloxetine, SET (1); flibanserin, 5-HT_{1A} (1); fluoxetine, SET (1.1); fluvoxamine, SET (2.3); imipramine, SET (1.41); levomilnacipran, SET (11.2); milnacipran, SET (9); mirtazapine, Hr (0.14), nafazodone, H1 (6); nortriptyline, NET or H_1 (4.35); paroxetine, SET (0.1); reboxetine, NET (7); sertraline, SET (0.3); trazodone, 5-HT_{2A} (7.7); venlafaxine, SET (102); vilazodone, SET (0.1); vortloxetine, SET (1.6). Flibanserin and milnacipran are not labeled for antidepressant activity. They were initially developed and tested for this indication but clinical trials were not supportive. In the case of milnacipran, its active enationer, levomilnacipran, was successfully developed for an antidepressant indication[2,14]

not being discussed here. That is the reason why most of the psychiatric drugs approved from 2009 to 2016 (Table 1.3) had the same well-established mechanisms of action [9].

With that said, there have been six novel mechanisms of action drugs developed and approved over the last 25 years (Table 1.4) [7]. These drugs may point the way to the future because of common features in their development. First, they were directed at a single behavior of symptom rather than a syndrome or cluster of behaviors and symptoms which may have different mechanisms mediating them. Second, the circuitry underlying the disturbance was relatively simple and well established. Third, the outcome variable was relatively dichotomous (e.g., smoke, don't smoke) rather than a reduction in a rating scale based on a compilation of the various disparate symptoms of a syndromic diagnosis such as MDD (e.g., the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale). As knowledge of the biology underlying MDD continues to improve, it will guide the development of mechanistically new antidepressants.

The other plus is that high-throughput screening can make new medications highly selective for their desired target. That is illustrated by the development done with tasimelteon and suvorexant which were screened against 200 targets which were not desired targets of the drug Table 1.5 [10]. The molecules, tasimelteon and suvorexant, were taken forward both because they affected their desired target at nanomolar concentrations and did not affect any of these other non-desired targets even at micromolar concentrations (i.e., 1000 times greater than the concentration needed to bind to their desired target).

Table 1.3 Psychiatric and selected CNS drugs approved 2009–2016

Year	Total drugs approved	CNS drugs	Psychiatric and selected CNS drugs	Specific psychiatric or CNS drugs generic/brand name (manufacturer)[a,b,c]	Labeled indication	Mechanism of action[d]	Substrate for drug transporter	Substrate for drug metabolizing enzymes
2009	26	4	3	Iloperidone/Fanapt (Vanda)[b]	Schizophrenia	5-HT2A > alpha-1 > D_2 (1:2:17)	Not P-gp; otherwise	CYP3A4 > CYP 2D6 ¼ carbonyl reductase
							NA	
				Asenapine/Saphris (Allergan)[b]	Schizophrenia and manic or mixed episodes of bipolar I disorder	5-HT2C > 5-HT2A > alpha-1 > D_2 (1:3:4:7)	NA	CYP1A2
				Milnacipran/Savella (Allergan)[c]	Fibromyalgia	SET > NET (1:8)	NA	Mainly excreted unchanged with little to no drug metabolism
2010	21	1	1	Lurasidone/Latuda (Sunovion)[b]	Schizophrenia and depressed phase of bipolar I disorder	5-HT2A ¼ 5-HT7 > D_2 (1:1:2)	NA	CYP3A4
2011	28	5	1	Vilazodone/Viibryd (Allergan)[b]	Major depressive disorder	SET > 5-HT1A (1:21)	NA	CYP3A4 > > 2C19 ¼ 2D6
2012	39	3	1	Locaserin.Belviq [Arena Pharm (US distributor: Eisai)][c]	Weight management/ obesity	5-HT 2C > 5-HT2A > 5-HT2B receptors (1:7:11)	NA	Multiple CYP and non-CYP pathways
2013	27	4	2	Vortioxetine/ Brintellix (Takeda)[b]	Major depressive disorder	SET > multiple 5-HT receptors (1 ≤ 10)	NA	CYP2D6 > > CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8, and CYP2B6

(continued)

Table 1.3 (continued)

Year	Total drugs approved	CNS drugs	Psychiatric and selected CNS drugs	Specific psychiatric or CNS drugs generic/brand name (manufacturer)[a,b,c]	Labeled indication	Mechanism of action[d]	Substrate for drug transporter	Substrate for drug metabolizing enzymes
				Levomilnacipran/ Fetzima (Allergan)[b]	Major depressive disorder	SET > NET (1:8)	NA	Mainly excreted unchanged
2014	42	4	3	Suvorexant/ Belsomra (Merck)[c]	Onset and maintenance of sleep	Orexin 1 and 2 receptors	NA	CYP3A4
				Tasimelteon/Hetlioz (Vanda)[c]	Non-24-h sleep- wake disorder	MT-1 and −2 receptors	NA	CYP1A2, 3A4, and phenolic glucuronidation
				Bupropion plus naltrexone/Contrave (Orexigen)[a]	Weight management in obesity	Bupropion: DAT > SET > NET (1:17:95); for naltrexone, see note below[e]	NA	CYP2B6 (bupropion); non-CYP enzyme (naltrexone)
2015	45	4	4	Proaripiprazole/ Aristada (Alkermes)[a]	Schizophrenia	D_2 > 5-HT1A > 5-HT2A (1:5:10)	NA	Same as aripiprazole (i.e., CYP3A4 and 2D6)
				Cariprazine/Vraylar (Allergan)[b]	Schizophrenia and manic or mixed episodes of bipolar I disorder	D3 > D2 ¼ 5-HT2B (1:6–8)	Not a substrate for multiple transporters	CYP3A4 > > 2D6
				Flibanserin/Addy (Sprout)[c]	Hypoactive sexual desire in premenopausal females	5-HT1A	NA	CYP3A4 > 2C19

				Brexpiprazole/ Rexulti (Otsuka)[b]	Schizophrenia and as an adjunct to antidepressants in major depressive disorder	5-HT1A > D_2 > 5-HT2A > alpha; 2C (1:3:4:5)	NA	CYP2D6 and 3A4
2016	26	2	1	Pimavanserin/ Nuplazid (Acadia)[b]	Psychosis in Parkinson disease	5-HT2A > 5-HT2C (1:5)	Not a substrate for multiple transporters	CYP3A4 and 3A5 > 2J2, 2D6, and various other CYP and FMO enzymes
Total	254	27	16					

Reproduced with permission from Preskorn [10]. © Preskorn 2017

CNS indicates central nervous system, *CYP* cytochrome P-450 enzyme, *D* dopamine, *DAT* dopamine transporter, *DOR* δ-opioid receptor, *FMO* flavin- containing monooxygenase, *gp* guinea pig, *H* histamine, *KOR* κ-opioid receptor, *M* muscarinic, *MOR* μ-opioid receptor, *MT* melatonin, *NA* not available, *NE* norepinephrine, *NET* norepinephrine transporter, *NME* new molecular entity, *P* porcine, *SET* serotonin transporter, *5-HT* serotonin

Of these 16 drugs:

[a]One was a combination of two existing drugs (bupropion+naltrexone); one was a prodrug of an existing molecule (proaripiprazole)

[b]Nine were NMEs approved for a psychiatric indication

[c]Five were NMEs approved for nonpsychiatric indications but which nevertheless targeted brain dysfunction (i.e., sleep, weight, or pain) with mechanisms of action that worked via the brain

[d]Numbers in parentheses in the mechanism of action column represent the relative binding affinity of the drug for these respective targets, with 1 being the highest binding affinity for the drug and the larger numbers being how much the concentration of the drug has to increase to affect the next target (with the general rule in pharmacology being that a drug is selective for a target if its next binding requires more than a tenfold increase in concentration). For more details, see Preskorn et al.[4]

Most of the drugs listed in the table are full antagonists at their respective receptors. The few exceptions are aripiprazole, brexpiprazole, and cariprazine, which are partial agonists at the D_2 receptor, and pimavanserin, which is an inverse agonist and antagonist at the 5-HT2A and 5-HT2C receptors (five times higher affinity for the 5-HT2A receptor than the 5-HT2C receptor)

[e]Naltrexone and its active metabolite 6β-naltrexol are antagonists at the MOR, to a lesser extent at the KOR, and to a far lesser and possibly insignificant extent, at the DOR. The K_i affinity values of naltrexone at the MOR, KOR, and DOR have been reported as 0.0825, 0.509, and 8.02 nM, respectively, demonstrating a MOR/KOR binding ratio of 6.17 and a MOR/DOR binding ratio of 97.2[5,6]

Table 1.4 Six central nervous system drugs with novel mechanisms of action developed in the past 25 years

Generic name	Brand name	Originator	Approval date	Latest PI revision	Indication(s)	Mechanism	Generic available
Ondansetron	Zofran	Glaxo	1/4/1991	9/18/2014	Chemotherapy-induced nausea and vomiting (CINV)	Serotonin 5-HT_3 receptor antagonism	7/2/2010
Aprepitant	Emend	Merck	3/27/2003	8/12/2014	CINV	Neurokinin (substance P)-1 receptor antagonism	7/24/2012
Ramelteon	Rozerem	Takeda	7/22/2005	3/1/2012	Insomnia[a]	Melatonin (MT_1, MT_2) receptor agonism	7/26/2013
Varenicline	Chantix	Pfizer	5/10/2006	10/15/2014	Smoking cessation	Acetylcholine nicotinic receptor alpha-4 beta-2 partial agonism	No
Lorcaserin	Belviq	Arena[b]	6/27/2012	6/27/2012	Weight loss	5-HT_{2c} agonism	No
Suvorexant	Belsomra	Merck	8/13/2014	N/A	Insomnia[c]	Dual orexin 1 and 2 receptor antagonism	No

Reproduced with permission from Preskorn [7]. © Preskorn 2014
PI package insert
[a]Difficulty with sleep onset
[b]Marketed by Eisai
[c]Difficulties with sleep onset and/or sleep maintenance

Table 1.5 Receptors for which tasimelteon (10 μm) did not inhibit or stimulate binding by >50%[a]

Adenosine A_1	Dopamine D_1	Melanocortin MC1	Rolipram
Adenosine A_{2A}	Dopamine D_{2L}	Melanocortin MC_3	Ryanodine RyR3
Adenosine A_3	Dopamine D_{2S}	Melanocortin MC_4	Serotonin 5-HT_1
Adrenergic α_{1A}	Dopamine D_3	Melanocortin MC_5	Serotonin 5-HT_{1A}
Adrenergic α_{1B}	Dopamine $D_{4.2}$	Motilin	Serotonin 5-HT_{1B}
Adrenergic α_{1D}	Dopamine D_5	Muscarinic M_1	Serotonin 5-HT_2
Adrenergic α_2	Endothelin ET_A	Muscarinic M_2	Serotonin 5-HT_{2A}
Adrenergic α_{2A}	Endothelin ET_B	Muscarinic M_3	Serotonin 5-HT_{2B}
Adrenergic α_{2C}	Epidermal growth factor	Muscarinic M_4	Serotonin 5-HT_{2C}
Adrenergic β_1	Erythropoietin EPOR	Muscarinic M_5	Serotonin 5-HT_3
Adrenergic β_2	Estrogen Erα	N-formyl peptide receptor FPR1	Serotonin 5-HT_4
Adrenergic β_3	Estrogen Erβ	N-formyl peptide receptor-like FPRL1	Serotonin 5-HT_{5A}
Adrenomedullin AM_1	G protein-coupled receptor GPR103	Neurokinin NK_1	Serotonin 5-HT_6
Adrenomedullin AM_2	G protein-coupled receptor GPR8	Neuromedin U NMU_1	Sigma σ1
Aldosterone	$GABA_B$	Neuromedin U NMU_2	Sigma σ2
Anaphylatoxin C5a	$GABA_{B1A}$	Neuropeptide Y, Y_1	Sodium channel, site 2
Androgen	$GABA_{B1B}$	Neuropeptide Y, Y_2	Somatostatin sst1
Angiotensin AT_1	Gabapentin	Neurotensin NT_1	Somatostatin sst2
Angiotensin AT_2	Galanin GAL1	Nicotinic acetylcholine	Somatostatin sst3
Apelin (APJ)	Galanin GAL2	Nicotinic acetylcholine α1	Somatostatin sst4
Atrial natriuretic factor	Glucocorticoid	Nicotinic acetylcholine α7	Somatostatin sst5
Bombesin BB1	Glutamate, AMPA	Opiate δ (OP1, DOP)	Tachykinin NK_1
Bombesin BB2	Glutamate, Kainate	Opiate κ (OP2, KOP)	Tachykinin NK_2
Bombesin BB3	Glutamate, NMDA	Opiate μ (OP3, MOP)	Tachykinin NK_3
Bradykinin B_1	Glycine, strychnine- sensitive	Orphanin ORL_1	Thromboxane A_2
Bradykinin B_2	Growth hormone secretagogue	Phorbol ester	Thyroid hormone
Calcitonin	Histamine H_1, central	Platelet activating factor	Thyrotropin releasing hormone
Calcitonin gene- related peptide $CGRP_1$	Histamine H_2	Platelet-derived growth factor	Transforming growth factor-β
Calcium channel L-type	Histamine H_3	Potassium channel [K_A]	Transporter, adenosine
Calcium channel N-type	Histamine H_4	Potassium channel [KATP]	Transporter, choline

(continued)

Table 1.5 (continued)

Cannabinoid CB_1	Hypocretin (orexin) receptor 1	Potassium channel [SK_{CA}]	Transporter, dopamine
Cannabinoid CB_2	Hypocretin (orexin) receptor 2	Potassium channel HERG	Transporter, GABA
Chemokine CCR1	Imidazoline I_2, central	Progesterone	Transporter, monoamine
Chemokine CCR2B	Inositol trisphosphate IP_3	Progesterone PR-B	Transporter, norepinephrine
Chemokine CCR4	Insulin	Prostanoid CRTH2	Transporter, serotonin
Chemokine CCR5	Interleukin IL-1	Prostanoid DP	Tumor necrosis factor
Chemokine CX3CR1	Interleukin IL-2	Prostanoid EP_2	Urotensin II
Chemokine CXCR2 (IL-$8R_B$)	Interleukin IL-6	Prostanoid EP_4	Vanilloid
Cholecystokinin CCK_1 (CCK_A)	Leptin	Prostanoid, thromboxane A_2	Vascular endothelial growth factor
Cholecystokinin CCK_2 (CCK_B)	Leukotriene (LTB_4)	Purinergic P_{2X}	Vasoactive intestinal peptide
Colchicine	Leukotriene, cysteinyl $CysLT_1$	Purinergic P_{2Y}	Vasoactive intestinal peptide 1
Corticotropin releasing factor CRF_1	Leukotriene, cysteinyl $CysLT_2$	Retinoid X receptor RXRα	Vasopressin V_{1A}
			Vasopressin V_{1B}
			Vasopressin V_2
			Vitamin D_3

[a]Reprinted from Lavedan et al. [2] under a Creative Commons license

Standard radioligand binding and enzyme inhibition assays were performed on receptors, binding sites, or enzyme systems obtained from various sources, including human, rat, mouse, guinea pig, rabbit, hamster, and bovine tissues (see Lavedan et al. [2], Supplemental Information), using the profiling screen and discovery screen panels (Panlabs) which consisted of 56 radioligand binding assays and 7 enzyme assays, respectively, and the SpectrumScreen panel (MDS Pharma Services) that included 170 pharmacological relevant targets (see Lavedan et al. [2], Supplemental Information). In addition, the $GABA_A$ benzodiazepine and $GABA_B$ binding sites were also tested independently (Panlabs biochemical pharmacology assays). Tasimelteon was used at a concentration of 10 μm except for two enzyme assays (protein kinases C: PKCα and PKCβ) where it was used at 100 μm and for the melatonin receptors in the SpectrumScreen panel where four concentrations (10 nm, 0.1 μm, 1 μm, and 10 μm) were tested. A response was considered significant if there was ≤50% inhibition or stimulation for the assays

The affinity of tasimelteon (10 μm) for the human hypocretin (orexin) receptor 1 expressed in transfected CHO cells and for the human hypocretin (orexin) receptor 2 expressed in transfected HEK-293 cells was determined in radioligand binding assays (Eurofins Cerep SA, Celle l'Evescault, France)

1.5 The Immediate Future Which is Upbeat

Between that development and the near future, ketamine and related drugs are the first legitimate hope for a new approach to treating patients with the form of MDD which is not responsive to biogenic amine antidepressants. While the antidepressant activity of ketamine and related drugs was initially discovered by chance as was the case with TCAs and MAOIs, it appears nevertheless to be robustly and rapidly effective in approximately 60% of patients whose depressive disorder is not responsive to biogenic amine antidepressants.

This new era will not simply hold the promise for treating those patients but also provide biological insights into these different forms of the major depression: (a) those responsive to biogenic amine antidepressants, (b) those not responsive to biogenic amine antidepressants but to glutaminergic antidepressants such as esketamine, and (c) those not responsive to either of these forms of treatment. The ability to divide patients with the syndrome of major depression into these three categories has the potential to permit understanding the biological reasons for why they fall into those three groups. The knowledge gained from that and from the mechanisms underlying the response to esketamine will in turn lead to new developments just as was true the development of SSRIs and SNRIs from the knowledge gained from studies of TCAS and MAOIs.

The figures and tables in this chapter come from the articles below. Each of these articles has its own reference list which the interested reader can access either through PubMed or on the Lippincott Williams & Wilkins website.

References

1. Kraepelin E. In: Barclay RM, Robertson GM, editors. Dementia praecox and paraphrenia. Huntington NY: Krieger; 1915.
2. Lavedan C, Forsberg M, Gentile AJ. Tasimelteon: a selective and unique receptor binding profile. Neuropharmacology. 2015;91:142–7.
3. Preskorn SH. The future and psychopharmacology: potentials and needs. Psychiatr Ann. 1990;20(11):625–33.
4. Preskorn SH. CNS drug development. Part I: the early period of CNS drugs. J Psychiatr Pract. 2010a;16(5):334–9.
5. Preskorn SH. CNS drug development: part II: advances from the 1960s to the 1990s. J Psychiatr Pract. 2010b;16(6):413–5.
6. Preskorn SH. CNS drug development: part III: future directions. J Psychiatr Pract. 2011;17(1):49–52.
7. Preskorn SH. CNS drug development: lessons from the development of ondansetron, aprepitant, ramelteon, varenicline, lorcaserin, and suvorexant. Part I. J Psychiatr Pract. 2014;20(6):460–5.
8. Preskorn SH. CNS drug development: lessons learned part 2. Symptoms, not syndromes as targets consistent with the NIMH research domain approach. J Psychiatr Pract. 2015;21(1):60–6.

9. Preskorn S. Psychiatric and central nervous system drugs developed over the last decade: what are the implications for the field? J Psychiatr Pract. 2017a;23(5):352–60.
10. Preskorn S. CNS drug development, lessons learned, part 4: the role of brain circuitry and genes – tasimelteon as an example. J Psychiatr Pract. 2017b;23(6):425–30.
11. Preskorn S. Drug-drug interactions with an emphasis on psychiatric medications. West Islip: Professional Communications, Inc; 2018.
12. Preskorn SH, Baker B. The overlap of DSM-IV syndromes: potential implications for the practice of polypsychopharmacology, psychiatric drug development and the human genome project. J Psychiatr Pract. 2002;8(3):170–7.

Chapter 2
The History of Drug Development in Psychiatry: A Lesson in Serendipity

Abhishek Wadhwa

Abstract The goal of this book is to provide a guide on modern day drug development in psychiatry. However, in order to understand current practices in drug development, it is important to first understand the history of psychiatry including early attempts at drug discovery and develoment. The early history of psychiatry is mired with the use of inhumane experimental treatments and the institutionalization of patients in asylums. Some of the earliest drugs used in these asylums were meant to sedate patients rather than treat underlying mental disorders. The earliest identified drugs treating mental disorders were born out of serendipitous discoveries which later led to their clinical effects being demonstrated through clinical trials and case studies. This is evident from the history of chlorpromazine, monoamine oxidase inhibitors, tricyclic antidepressants, lithium, and others. We discuss in detail about each of these psychotropic drugs, the events leading up to their discovery, and their role in formulating the biological basis of mental disorders including schizophrenia, depression, and bipolar disorder. Psychiatry, it seems has worked its way backwards from first identifying treatments before understanding the biological basis of mental disorders, in a sharp contrast to the other fields of medicine. With our growing understanding of the etiopathogenesis of mental disorders, drug development in psychiatry is evolving to develop treatments that target the underlying physiology of mental disorders.

Keywords History · Psychopharmacology · Serendipity · Mental disorders · Catecholamine · Dopamine · Antipsychotic · Antidepressants · Drug development

2.1 Introduction

Psychiatry has evolved over time in terms of how mental disorders are conceptualized and how biological treatments are used and developed. The focus of this book is on the development of biological treatments for mental disorders. In order to

A. Wadhwa (✉)
University of Alabama at Birmingham, Department of Psychiatry and Behavioral Neurobiology, Birmingham, AL, USA
e-mail: abhishekwadhwa@uabmc.edu

M. Macaluso et al. (eds.), *Drug Development in Psychiatry*, Advances in Neurobiology 30,
https://doi.org/10.1007/978-3-031-21054-9_2

understand drug development in psychiatry, one must begin with an understanding of the historical underpinnings of the field. The term psychiatry ("Psychiatrie") was first introduced by Johanne Christian Reil, professor of therapy at the University of Halle, in Germany in 1808. Reil, in his paper, argued that the cause of human disease is an essential interaction among the three domains of mental, chemical, and physical. The term "psychiatry" refers to a medical discipline rather than a philosophical or theological one [1]. Benjamin Rush is often considered the father of American psychiatry [2]. He is reported to have considered psychiatry as part of the field of medicine and devoted a large part of his teachings to the same. Building upon these concepts, Chiarugi, in Florence, for the first time suggested treating mental disorders using an approach which is respectful of patients and advocated for humane treatment. Jean-Baptiste Pussin and Philippe Pinel used this approach to institute "moral treatment" (1801), which was a psychological treatment and a sharp contrast to the violent treatments often used in asylums of the nineteenth century. Pinel further refined this approach into a "medical moral treatment." This approach included reward-based activities, physical exercise, and offering nutritious food to patients while limiting the use of physical restraints. Pinel and Pussin reported a high success rate with "mortal treatment" and inspired American psychiatry to follow the same approach [3]. The concept of "medical moral treatment" inspired Dorothea Dix who became a leading figure of national and international movements to promote the safe and humane treatment of people with mental disorders. Dix played a vital role in establishing and expanding state funded facilities for the treatment of mental disorders. By 1860, 28 out of 33 states in the USA were reported to have at least one public psychiatric hospital [4, 5].

The second and third decades of the twentieth century saw major changes in the understanding of mental disorders by the general public and medical community. It was during this time that the somatic origins of mental disorders began being systematically evaluated [5]. This was also the time where prefrontal lobotomy was developed as a treatment. Prefrontal lobotomy was first introduced in the USA in 1937 and was widely used until the early 1950s before the release of chlorpromazine. Lobotomy was heavily criticized due to being invasive, inhumane, and permanently changing the personality of patients [6, 7]. Electroconvulsive therapy (ECT) was developed in 1938 by Cerletti and was extensively used in the US in its unmodified form. The use of ECT declined in the 1960s due to a number of factors including the introduction of antidepressant drugs as well as the negative and often inaccurate depiction of ECT in the media [8]. After World War II, psychoanalysis emerged with Freud's theories gaining mainstream popularity [5].

Historically, there is documented use of psychotropics since long before the introduction of psychiatry into the practice of medicine. Ancient Greek and Indian civilizations documented the use of psychoactive substances to experience euphoria. The concept of using a drug for understanding mental disorders is reported to have been conceived by the French psychiatrist, Moreau De Tours (1845) [9]. Emil Kraeplin (1892) used the term "pharmacopsychology" to indicate the effects of drugs on psychological functioning. Kraeplin is reported to be among the first to promote the idea of treatment response to determine the clinical effect of a drug.

Sigmund Freud is also regarded as an early figure in psychopharmacology as indicated in his famous letter to Maria Bonaparte, where he predicted that the way to understanding psychosis and would be guided by organic chemistry or access to it through endocrinology. These developments took place around the same time that a paper was published to describe the antipsychotic actions of Rauwolfia which had been utilized in Indian folk medicine for a very long time. This paper was published in an Indian medical journal and was largely overlooked by Western medicine [9]. The nineteenth century also saw the use of sedatives and hypnotics including drugs such as narcotics, chloral hydrate, and bromides, primarily to sedate and calm patients but not to treat specific mental disorders [10].

Moving into the twentieth century, the serendipitous discovery of several psychopharmacologic agents lead to the development of major classes of drugs to treat mental disorders. The focus of this chapter is on historical aspects of drug development, with a focus on serendipitous discovery. Other chapters in this book will focus on the use of structure activity relationships and animal models to further develop drugs for treating mental disorders. The book will also focus on modern approaches to drug development including reverse engineering, the role of neuroimaging, and the use of biomarkers including genetic and epigenetic markers in drug development research.

2.2 Chlorpromazine

The serendipitous discovery of chlorpromazine was an early development for the budding field of psychopharmacology. Phenothiazines were developed in the late nineteenth century for use in the dye and textile industries. At the time, phenothiazines were recognized for their antiseptic and active parasitic properties and were further explored for their antihistaminic properties in the early twentieth century. In the 1930s and 1940s, there was interest in producing synthetic histamines for use in medical research. The pharmaceutical division of a French company, Rhône-Poulenc, in collaboration with research groups at the Pasteur Institute developed novel antihistamines based loosely on diphenhydramine. Paul Charpentier, a chemist at the company, modified and tested the antihistaminic properties of several phenothiazine compounds. One of his earlier successes was promethazine in 1947. Henri-Marie Laborit, a French surgeon, was experimenting with antihistamines for use in preventing surgical shock in the 1940s by creating a form of artificial hibernation by reducing hyperthermia. When Laborit administered promethazine to his patients he observed a unique psychological phenomena that he termed “euphoric quietude.” The cardinal features of “euphoric quietude” included (1) weak and reversible narcosis, (2) no clouding of consciousness, and (3) emotional indifference [10–12].

Simone Corvoiser, at Rhône-Poulenc, analyzed the sedative properties of the antihistaminic agents synthesized by Paul Charpentier and his team, identifying promethazine as a promising option. Charpentier continued to work on further