Chapter 5
Drug Development for New Psychiatric Drug Therapies

M. Lynn Crismon, Janet Walkow, and Roger W. Sommi

Abstract Drug development is an expensive, high risk, and highly regulated process. Only about 6.2% of new molecules tested for mental disorders eventually achieve Food and Drug Administration (FDA) approval. New molecular entities are produced, and extensive in vitro animal testing is performed before they are evaluated in humans. The compound is used in animals to predict clinical effects in humans, and studies addressing pharmacodynamics, pharmacokinetics, toxicology, and mutagenicity are conducted. Human research proceeds in three stages with the ultimate goal of proving that a new agent is efficacious and safe for a treatment of a specific disease in humans. If efficacy and safety are demonstrated in two Phase III studies, then the sponsor can submit a new drug application (NDA) to the FDA. The FDA oversees each step of the process to assure that good research practices are followed, data integrity is assured, and human research subjects are protected.

Keywords Drug development · Clinical trial · FDA · Biomarker · Animal models · Psychotropic · Regulation · Pharmacokinetics · Pharmacodynamics · Efficacy · Safety

Innovations in healthcare products or services have the potential to positively impact society; however, taking an early discovery or idea to the clinic is a daunting challenge. Along the way, these technologies face roadblocks unique to healthcare. The drug development pathway (Fig. 5.1) details the various steps and regulatory requirements that guide the development of new psychiatric drug therapies. A strong

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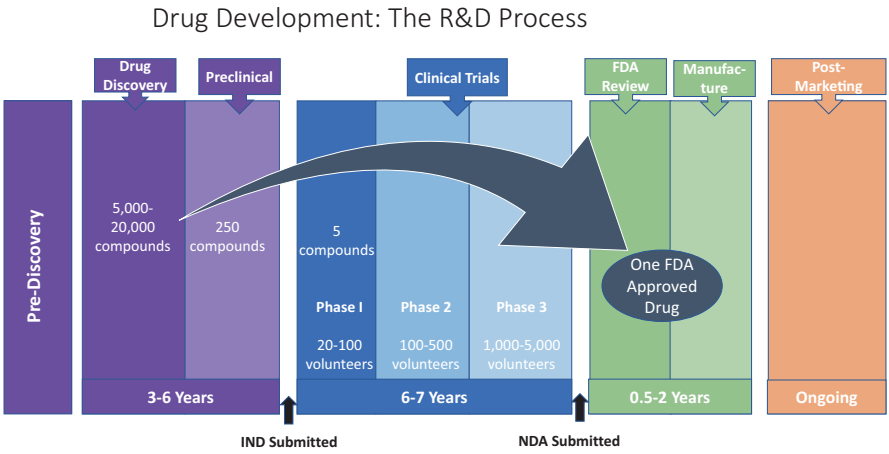

Fig. 5.1 The research and development process. Adapted from the American Association for Cancer Research [3]

understanding of the processes, regulatory requirements, timelines, and the impact they have on developing and commercializing new psychiatric drug products is essential for understanding the timing, cost, and complexity involved for each product that is commercialized. The goal of drug development is to find and provide new drugs that we can depend on to improve our health and quality of life.

Psychotropic medications are used to treat the symptoms associated with a variety of mental disorders. These therapies exert effects on the brain and nervous system, as well as other organ systems, and they undergo extensive development and testing before becoming a prescription product. The pathway for new drug therapies to be approved by the Food & Drug Administration (FDA) is highly regulated to ensure the efficacy, safety, and quality of these medicines. Understanding the steps involved, the clinical components, and the FDA's role in approving new psychiatric therapies provides important context for researchers, clinicians, and other health professionals.

The information presented in this chapter reflects the current US practices and regulatory guidelines unless otherwise noted.

5.1 The Drug Development Pathway

Drug development starts with discovery of a new molecule which, if successful, proceeds through in vitro studies, animal studies, studies in healthy individuals, and proceeding to studies in people with the disorder of interest. If found to be both efficacious and safe, then a new drug application is submitted to the FDA.

5.1.1 Pathway Overview

There are four distinct stages of the pathway for developing new drug therapies. The process for evaluating and identifying the best candidates to advance is time-consuming and expensive. It can take between 10 and 14 years and cost billions to develop a therapy with the characteristics to achieve a specific, desired result.

The earliest stage, *discovery/preclinical***,** includes all of the activities before a new drug therapy advances into human clinical trials. The first part, *drug discovery*, involves researchers scanning up to tens of thousands of potential compounds before identifying lead candidates for a specific disease. This process identifies up to 250 compounds to move forward for more detailed evaluation.

The lead candidates progress to the *preclinical* phase for further characterization, experiments, and formulation development into the most suitable forms for the specific treatment, including a tablet, capsule, orally dissolving tablet, injectable, intravenous solution, topical patch, or inhaled product. As potential drug candidates go through this stage, the number narrows to a limited number (five or fewer) that will advance into clinical trials. Once the preclinical work has progressed sufficiently, an *investigational new drug (IND)* application is filed. The FDA reviews the application and decides whether there is enough information to allow a product to proceed to human clinical trials. Only those with the best potential to achieve specific clinical results will move into this stage.

Once a product is approved by the FDA to enter *clinical trials*, a *clinical development plan (CDP)* is developed and reviewed with the FDA to define how the clinical trials will be conducted. The clinical trials consist of three stages, typically starting with a small group of healthy volunteers (Phase I) to determine the safety and basic pharmacokinetics of the test product, to large studies involving hundreds to a thousand or more patients at multiple study sites (Phase III). In order to progress from one phase to the next, the FDA must review the data and decide whether to allow the studies to progress to the next phase.

The third stage that encompasses regulatory review by the FDA is the manufacturing processes. These activities take place as early as the drug discovery and preclinical phases. Throughout the development pathway, regulatory activities and efforts to scale up production of the *active therapeutic ingredient (ATI)* as well as the final formulation are occurring. The i*nvestigational new drug (IND)* application is filed during the preclinical phase, and a *new drug application (NDA)* can be filed with the FDA for review and potential approval following completion of Phase III clinical trials. From the original thousands of compounds identified in the discovery phase, only one will typically make it all the way through the process and be approved by the FDA for commercialization.

Following the approval of a new drug product, ongoing monitoring of compliance with manufacturing and distribution processes must occur. In addition, information concerning adverse effects is collected over a long period of time. Clinical trials are limited to hundreds to perhaps over a thousand people, and it is often not obvious which adverse effects are most prominent or problematic until many more

patients have been treated. It may take years to answer whether certain adverse effects, particularly those that are rare but potentially serious, are problematic and those effects are addressed in the fourth stage that is often referred to as Phase IV, *post-marketing surveillance programs*, which assess patient safety and quality of life as well as drug product effectiveness.

5.1.2 Drug Development Costs

As indicated in Fig. 5.2, developing new drug therapies is a massive investment in time and resources. In the 1980s, the cost to develop a new drug product was approximately $100 million. A 2014 report found the cost to develop a prescription drug had reached $2.6 billion [20]. Over four decades the cost has risen exponentially. Examination of the cost per development stage reveals small increases in discovery, accelerating costs in preclinical, and the most significant increases occurring in the clinical trials (Phases I, II, and III). Only launch and discovery costs appear to have decreased, likely attributed to the reduced costs of digital advertising and newer, high-throughput screening tools used in early discovery [20]. Part of this cost is driven by the fact that only about 9.6% of all compounds across all therapeutic areas are FDA approved and reach the market. This is even lower in psychiatry (6.2%) and neurology (8.4%). The Phase III clinical trials' failure rate with central nervous system (CNS) acting agents is significantly higher than with other types of agents, and it is estimated that the Phase III clinical trial failure rate is 20% higher than in other therapeutic areas [39]. This has prompted pharmaceutical companies to be both cautious and strategic in deciding the types of compounds to develop. [38, 69].

Since the 1990s, drug development costs have more than doubled, with the largest cost increase being in human clinical trials. Adapted from O'Hagan [59], Life Size VC [53], Policy and Medicine [61].

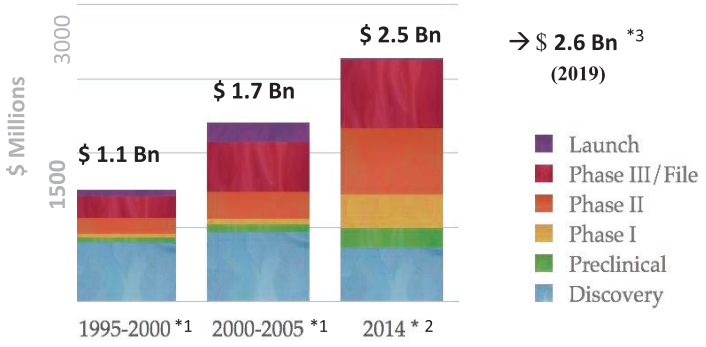

Fig. 5.2 Increase in drug development costs over time

Between 2009 and 2018, it was estimated to cost between $314 million and $2.8 billion to bring a new therapeutic entity to market, including the capitalized R&D cost per product and expenditures on failed trials [77].

5.1.3 Regulatory Overview

The approval pathways for drug therapies can be complex, time-consuming, and expensive. The regulatory tools that have been developed to certify compliance and efficacy of new medicines are designed to ensure the safety and integrity of every product before it can be approved for commercialization. Most take for granted that drug therapies are safe if they are approved for commercialization and sale – a good assumption since FDA's involvement starts early in the development process and continues after a product is commercialized.

The FDA becomes involved in the preclinical phase, when the sponsor identifies a lead molecule and plans to prepare for testing its therapeutic potential in human clinical trials. This is when regulations become a prominent part of developing the strategy for advancing a product.

The regulations that are required or authorized by statute are published in the Federal Register, the US government's official publication for notifying the public of agency actions. The procedures that health innovators follow come from US laws, executive orders, and FDA regulations that can be found in the Code of Federal Regulations (CFR). Regulations that apply to the FDA's oversight of food and drugs are found in Section 21 of the CFR [15]. These regulations document all actions required of drug sponsors under federal law.

To better understand how FDA regulations align with the R&D timeline, the development pathway is depicted in Fig. 5.3, including the key regulatory elements as they relate to the development pathway.

Drug development is a highly regulated process, with the Food and Drug Administration carefully monitoring and evaluating each step of the process. Developed from [28].

These will be discussed in greater depth in the preclinical, clinical, regulatory, and post-marketing sections.

5.1.4 Types of Drug Therapies

Drug therapies fall into several categories: new molecular entities (NME), therapeutic biologics, generics, biosimilars, over-the-counter (OTC) drugs, vaccines, blood products, and cellular and gene therapy products. New psychiatric drug products are currently prescription products in the NME category.

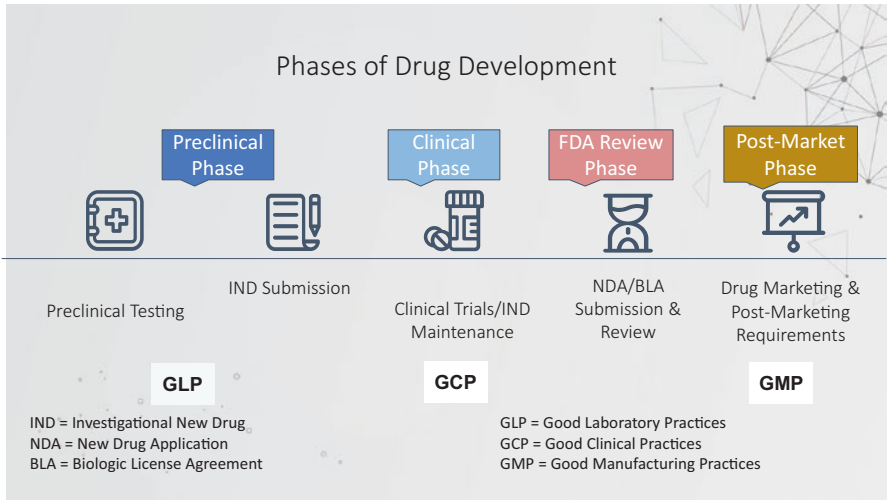

Fig. 5.3 Regulatory components of drug development

New Molecular Entities

The development and approval of new molecules and biological therapies are handled by CDER. This FDA branch also oversees nonprescription, or OTC drugs as well as the process for moving an approved prescription (Rx) product to OTC status, called an *Rx-to-OTC switch*.

Generics

Generics are copies of innovator or brand-name prescription drugs and comprise almost 90 percent of all prescriptions dispensed in the United States [7]. Generic drug developers are allowed to use data generated by brand-name companies for efficacy and safety, resulting in significantly lower development costs and lower prices for patients. The Hatch-Waxman Act of 1984 established patent exclusivity protections for drug innovators and granted generic companies access to regulatory approval by filing an abbreviated NDA (ANDA). To achieve FDA approval, the manufacturer must demonstrate that the generic product has bioavailability similar to the innovator product. To be considered bioequivalent, the generic product must have a peak plasma concentration, time to peak plasma concentration, and total amount of drug absorbed (area under the curve) that is not statistically different from the innovator's product. These studies are typically crossover studies in a small number of healthy male subjects, using the subject as his own control

5.2 Preclinical Drug Development Phase

The preclinical phase is a robust transition with the overall goal of predicting whether a compound will be beneficial in treating a particular disease. Activities focus on evaluating drug molecules from the discovery phase.

5.2.1 Characterization

A primary job of the pharmaceutical formulation scientist is determining how best to formulate and deliver a compound to its site of action in the body, while ensuring that it remains stable over time. The starting point of this process focuses on obtaining a greater understanding of the lead compound itself and determining the physical and chemical properties of the lead compound. Larger quantities of the drug molecules are made so that they can be tested to gauge their solubility in various liquids, sensitivity to light or heat, chemical stability, and interactions with other materials.

All of these important properties need to be evaluated and addressed before attempting to incorporate an active compound into a dosage form. These answers play a large role in the stability of a dosage form, how available it is at its target site of action, the most appropriate storage conditions, and how the drug product should be manufactured.

5.2.2 Developing a Formulation Prototype

Characterizing the drug molecules, coupled with knowledge of the disease or condition being treated, as well as the patient population, informs the type of formulation that should be considered, whether it is preferred as a tablet, capsule, orally disintegrating tablet, injectable, inhaled product, nasal spray, topical cream/ointment, or transdermal patch. The selection is based on the drug's chemical and physical properties with consideration of patient population needs. Another consideration is the release rate – whether a rapid release or extended release formulation is preferred to reach appropriate dosing levels in a specific clinical condition. Patient adherence may be impacted by the dosing schedule, and extended release products that require only daily or twice daily doses can be helpful for medication adherence. Similarly, long-acting injectable products may allow parenteral administration every few weeks or months.

In psychiatry, several interesting developments occur beyond oral formulations that are directed at specific clinical management challenges. Specifically, it is important to address administration of medications during an acute crisis where patients may be combative and uncooperative and treatment nonadherent. Other formulations may address either tolerability or unique oral absorption challenges.

Some examples of strategies to counter the acute crisis situation are the use of oral solutions and orally disintegrating tablets – where the clinician has some confirmation that the patient has actually swallowed the medication or that the drug will be absorbed through the oral mucosa. Immediate acting injections allow quick onset but may be less acceptable to patients. Other novel formulations include inhaled loxapine [19] which results in rapid absorption and onset of action.

Challenges with overcoming barriers with medication adherence have been addressed principally with improving the drug's tolerability and the development of long-acting injectable (LAI) formulations. In psychiatry most of the LAI development has been with antipsychotics. LAI development incorporates molecular strategies including using prodrugs (esters) and/or physical strategies of using oils, polymers, gels, and manipulation of particle size with the ultimate goal of delaying absorption to the point the drug can be administered in intervals of weeks to months. Marketed products include the use of esterified molecules delivered in sesame oil, drug molecules trapped in glycolide/lactide microspheres, crystallization and grinding processes to create various particle sizes of relatively insoluble ester salts, and the use of gels which essentially form an implant that slowly dissolves and releases drug.

Challenges to counter absorption and tolerability include the use of patches and sublingual formulations. Selegiline patches allow for the absorption of the drug with clinically relevant CNS concentrations while minimizing the inhibition of MAO-A in the gut – improving the tolerability and limiting the risk of dietary tyramine interactions [18]. Asenapine is available as a sublingually absorbed formulation as the bioavailability is drastically reduced if swallowed. More recently, an asenapine patch formulation allows for absorption of the drug without the issue of dysgeusia limiting its use. Other antipsychotic patch formulations are currently in development [1]. In addition to solving issues around oral absorption, administration in a crisis, or enhancing adherence, the use of oral solutions, orally disintegrating tablets, and patches provides a pathway to drug administration for patients unable to swallow capsules or tablets or who are restricted from taking medications orally.

The use of prodrugs is another method to potentially avoid drug related complications. A prodrug is inactive pharmacologically but is metabolized in the body to the active form. An example is lisdexamfetamine which is hydrolyzed in the blood to amphetamine. Lisdexamfetamine has potentially less abuse potential than amphetamine, even when administered intravenously [54].

5.2.3 In Vitro-in Vivo Testing

The material characterization and early formulation studies of a lead compound are performed using a variety of equipment and in vitro testing methods. These provide important information to assess whether to proceed to in vivo studies. This is a noteworthy transition point, as the in vivo studies require extensive knowledge and experience to design, conduct, and analyze the results.

Significant effort is taken in selecting formulations to include in the in vivo studies, as they require substantial time and cost commitments. The early and later stage pharmacokinetic-pharmacodynamic (PK-PD) studies will often begin with rodents and may expand to other, more specific animal models for the intended disease target. It is common for one or more formulations to be evaluated in the early in vivo studies to observe differences in effectiveness, tolerability, and adverse effects that can lead to choosing a lead formulation or deciding that it needs to be re-engineered.

At the same time, the in vivo studies are occurring, the formulations being tested in animals are often undergoing stability studies at various temperatures, light conditions, and humidity. These parallel activities can serve to expedite moving through the preclinical phase.

5.2.4 Pharmacokinetic-Pharmacodynamic (PK-PD) Analysis

The PK-PD analysis examines the drug concentration in a body compartment – most commonly venous blood – and relates it to the drug's effect. The bioanalysis provides an estimate of the molecule's safety and efficacy. Animal studies can provide a pharmacokinetic profile that shows how well the drug products are absorbed, distributed, metabolized, and excreted. Drug absorption refers to the percent of administered drug that ultimately reaches the circulation, also referred to as the drug's bioavailability. For example, intravenous medications have 100% bioavailability; however, other routes of administration and formulation are generally lower since they may be absorbed in the intestine or be subject to first pass metabolism in the liver. Bioavailability in preclinical and clinical studies is determined by plotting the blood concentration as a function of time and referred to as the area under the curve (AUC).

Biomarker selection and correlation with clinical endpoints are important for successful PK-PD modeling and provide predictive value in drug development, if they reflect the mechanism of action for intervention, whether or not they are surrogate endpoints [16]. Identification of biomarkers that can be used for predictive clinical assessment of disease progression can help measure the effect of drug interventions.

The results of the PK-PD studies provide information on how to refine drug administration, evaluating whether the dose needs to be adjusted or deciding if the formulation needs to be changed. The studies may show that the drug or its metabolites stay in the body a short time, making it necessary to take several doses a day or develop a sustained release formulation.

Psychotropic drug development has been limited in that a mental disorder diagnosis is based upon clinical phenotypes which likely represent substantial heterogeneity in etiology and pathophysiology [9]. In fact, the specific pathophysiology of mental disorders is currently unknown. Therefore, specific pharmacological mechanisms of action are used for heterogenous disorders. Serendipity has played a major role in the discovery of psychotropic medications, particularly during their first few decades of development. This is best represented by the fact that chlorpromazine was first investigated as a potential medication for "surgical shock" largely based upon its antihistaminic properties. Although ineffective for this purpose, the French surgeon Henri Laborit noted that patients experienced "no loss of consciousness, no change in the patient's mentality but a slight tendency to sleep and above all 'disinterest' for all that goes on around him" [71]. Based upon his observations, he encouraged psychiatrists to use it in patients with psychosis, and it was subsequently developed as the first modern era antipsychotic.

Animal Models

Animal models have significant limitations when used to study mental disorders and the effects of medications. Rodents do not express the same range of emotions as humans, and the neural circuits are not nearly as complex [65]. Traditionally, the animal models used to predict efficacy of a medication for a particular mental disorder were developed based upon a behavior, and if it affected that behavior, then the mechanism of action was explored [17]. For example, early animal models of antipsychotic effect were dependent on a drug's ability to produce catalepsy [58]. Thus, developed antipsychotics were almost guaranteed to produce extrapyramidal adverse effects in humans. More recently, computational chemistry has been used to predict the mechanisms that specific compounds will have. However, psychotropic drugs are largely still not developed based upon a known pathophysiology for a given disorder. Although it is hoped that genetics may ultimately allow psychotropics to be developed for homogenous disorders that is currently not reality [9].

Animal models typically involve rodents – rats or mice. The early developed animal models were based upon drugs that had been proven clinically effective. Thus, the models tended to predict efficacy for compounds that had similar mechanisms of action (e.g., action on the benzodiazepine receptor for anxiety and dopamine receptor antagonism for psychosis) [10]. Animal models are developed with the goal of having the following [10]:

- Face validity – the behavioral and physiological response in the animals is identical or at least very similar to that seen in humans.

- Predictive validity – drugs with clinical efficacy in a given disorder should produce the response in the animal model.
- Construct validity – the etiology of the behavior and the pathophysiology are similar in both the human and the animal model.

Animal models are challenging in that our understanding of the pathophysiology of mental disorders is inadequate, and human and rodent behaviors are much different. Many of the symptoms and behaviors seen in human mental disorders are not present in other animals. Much of the time, the animal model does not correspond with human emotions such as depression or anxiety, but rather examines certain kinds of locomotor behavior in different conditions. Thus, construct validity is highly suspect, and this may be one potential explanation for the high failure rate of CNS acting compounds in clinical trials. Similar challenges exist for face validity since the etiopathophysiology of most mental disorders is unclear, and humans and other species have different behaviors. Predictive validity is complicated by the fact that animal models are validated based upon existing FDA-approved psychotropics that for the most part have only modest efficacy. This is further complicated by compounds being assessed in animals acutely while pharmacotherapy in humans is typically several months to years. [39].

Select animal models are briefly discussed below.

Animal models for antipsychotics – Animal models involving the administration of either amphetamine or phencyclidine (PCP) are commonly used to screen compounds for potential antipsychotic effects. The amphetamine model is based upon the observation that amphetamine produces positive symptoms of psychosis in humans. Amphetamine produces excessive mesolimbic dopaminergic activity, resulting in spontaneous locomotor activity and stereotypy in animals. D_2 receptor antagonists block these effects [51]. Chronic amphetamine administration produces desensitization with resulting deficits in learning and attention. Both first- and second-generation antipsychotics have been shown to block desensitization.

Phencyclidine (PCP) produces both positive and negative psychotic symptoms in humans and may be a better model for the symptoms associated with schizophrenia. The attentional set-shifting test (ASST) is used to assess executive function in rodent models. The animals must learn a rule and then shift their attention to a previously irrelevant stimulus. NMDA antagonists such as ketamine produce positive and negative symptoms as well as cognitive deficits. These effects are attenuated by antipsychotics as well as nicotinic agonists. Some deficits are reversed by second generation but not first-generation antipsychotics. Animal models of cognition are more predictive of human cognition than models for symptoms such as delusions or hallucinations. Prepulse inhibition (PPI) looks at suppression of a strong stimulus by a small stimulus. Antipsychotics lessen the worsening of this response induced by NMDA receptor antagonists [51]. The Morris Water MAZE (MWM) assesses multiple cognitive functions, including learning, memory, and retention. The animal learns where a submerged platform is in a tank of water. Then the platform is moved or removed from the tank. PCP negatively affects performance on this test, and it is reversed by SGAs. Social interaction is assessed by placing unfamiliar rodents in a

lighted arena, and then the amount of time they spend interacting is measured. PCP impairs their social interaction [52].

Animal models for anxiety disorders – Anxiety disorders are complex, and no one animal model is appropriate for all anxiety disorders. Anxiety animal models can be divided into two groups. Conditional response models, such as the Geller-Seifter conflict model, involve the animal's response to painful or stressful stimuli. Unconditioned response models, such as the elevated plus maze model, involve the animal's natural response to stimuli that do not involve stress or pain [10]. Animal models for potential anxiolytic effect are limited by being based upon suppression of normal behavioral response rather than on decreasing pathological anxiety [39].

Animal models for depression – The forced swim test is a highly predictive animal model used to screen for antidepressant effect. The rat is placed in a vat of water and forced to swim to stay alive. Eventually, the rat will cease to swim and will only move enough to keep its head above water. This is commonly referred to as a "state of despair," but may more accurately be a learned adaptation [39].

Over the past 50 years, new psychotropics have primarily differed clinically by having different side effect profiles than older medications. In particular, SSRIs and other newer antidepressants are much less toxic in overdose situations than the tricyclic antidepressants. Clozapine is the one major exception, and it is unclear why clozapine reduces psychotic symptoms in many patients with schizophrenia who have not responded with other antipsychotics. If we want psychotropic drug development to produce more effective agents, it is critical that we have a better understanding of the basic neurological (as well as other systems) mechanisms underlying different human mental disorders. If successful, mental disorders could be classified based upon pathophysiology rather than symptom presentation [39].

New approaches may assist in our understanding of the pathophysiology of mental disorders and the development of future medications. Behavioral assessments that target a single neural circuit in both humans and other animals increase the utility of animal models. For example, stop signal reaction time has been used in both rodents and humans to demonstrate the effects of atomoxetine on decreasing impulsivity, and this is associated with activation of homologous areas of the inferior frontal cortex [73]. Thus, it is important to utilize animal behavioral models that have a human behavioral or cognitive counterpart. It has also been suggested that objective behavioral assessments should be incorporated into Phase II and III trials because they reflect the pharmacology of the drug and not just its effect on clinical symptoms [73].

Optogenetics can be used to visualize a genetically targeted neural circuit. This allows one to turn a neural circuit on or off. Artificial intelligence may also hold promise in being able to identify new biological targets and compounds for investigation [39]. The future may lie in the use of induced pluripotent stem cells (iPS cells) from patients with the disease of interest. These can be reprogrammed into almost any cell line and allow for the study of individual neurons with the same genetics as the patient. These can be further developed into cerebral organoids that resemble the developing human brain [65]. Patient-specific iPS cells can be

transplanted into rodent brains. In a schizophrenia model, human glial cells produced from iPS cells are transplanted into mice producing an animal where the majority of the glial cells are human. The chimeric mice develop decreased social interaction, anxiety, and decreased prepulse inhibition. This has potential for producing animal models to study drug action. Advances in our ability to study brain function and evaluate behavioral and cognitive function may lead to advances in our understanding of mental disorders as well as their treatment. This could potentially result in patient specific drug development. However, the cost of this would likely be prohibitive.

5.2.5 Mutagenicity

One of the nonclinical safety tests that must be performed prior to a new drug candidate's approval is assessing the drug's ability to cause changes to a cell's DNA sequence or mutagenicity [31]. These changes have been linked to a drug product's potential to cause cancer. These tests are performed using bacteria as well as mammalian cells and animals. The inactive ingredients in a formulation may also generate impurities as by-products of manufacturing or degradation during storage. This has led to the development of computer models based on chemical structure to aid in predicting the mutagenicity of both drug impurities and drug substance. These statistically-based Quantitative Structure-Activity Relationship correlations, or QSAR models, have been the subject of vigorous research by the FDA for predicting mutagenicity as well as other drug toxicities. There are now international guideliens [46] ratified by FDA and regulatory counterparts, that allow QSAR models to substitute for traditional laboratory tests for determining mutagenic of drug impurities.

5.2.6 Toxicology Considerations

Animal models are used in preclinical drug development to simulate what occurs in human biologic systems and evaluate endpoints of interest. Selecting the most appropriate animal models for conducting the formal Good Laboratory Practices (GLP) toxicology studies is critical for predicting human toxicity. While animal models are rarely 100 percent predictive, those that are physiologically similar to the endpoint of interest can guide researchers as long as there is a grasp of the similarities and variances of the model as it relates to humans.

Dose escalation studies can be used to explore the drug's toxicology. Specific negative effects on major organ systems (e.g., brain, heart, kidney, liver) can be examined at each dose. In addition, the lethal dose in 50% of the animals studied (LD_{50}) can be determined. Toxicology studies are typically conducted in rodents

(mice or rats) plus one other species (e.g., dogs, minipigs, primates, rabbits). Even when testing in multiple species, human organ toxicity can occur in the absence of toxicity in other species. [60].

Establishing the safety of lead products is a culminating activity of the preclinical phase. The toxicology studies – also referred to as safety assessment – represent a pivotal component of the information that undergoes regulatory review and leads to the FDA's go/no go decision for allowing a product to move forward into human clinical trials. Using appropriate animal models and methods for generating robust, reliable data will establish a toxicology profile for new drug candidates.

5.2.7 Regulatory Pathway: Preclinical to Clinical Trials

New drug development is a highly regulated, complicated process that requires specialists and intense research and development skill sets in the medical research community. All regulations and safety indications must be observed carefully, and human and animal clinical trial subjects treated professionally and with the utmost care.

The FDA's [33] evaluates new drugs before they are approved to be marketed and sold. The regulations that CDER enforces work to ensure that drug products are safe and effective and that their benefits outweigh any known risks. The formal animal toxicity studies (preclinical) and the application to enter clinical trials are subject to FDA regulations: Good Laboratory Practices (GLP) and the Investigational new Drug Application (IND) are discussed below.

The toxicity studies intended to support applications for entering human clinical trials must be conducted under GLP. The GLP describes the FDA regulations for in vivo and in vitro experiments subject to FDA safety review. Investigational drugs being evaluated in nonclinical safety studies must comply with GLPs. The regulation embodies a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, reported, and archived, covering the personnel, facilities, operations, and records that are involved in GLP studies.

GLPs are designed to provide regulatory guidance for ensuring the integrity of data from nonclinical studies. In the USA, the GLPs are administered by the FDA and are found in the Code of Federal Regulations [15]. These regulations cover the definitive preclinical studies that FDA reviews prior to making the final decision regarding approval to start testing in humans.

5.2.8 Investigational New Drug (IND) Application

Preclinical data are used as a basis to design the pivotal safety studies that will be included in the IND submission that is reviewed by CDER. As a new product undergoes preclinical evaluation, the sponsoring company collects data from a variety of

prescribed testing to demonstrate that the drug is safe and effective for its intended use. Prior to being tested on people, laboratory and animal testing is conducted to determine how the drug works, whether it is successfully treating the targeted disease, and if it appears to be safe.

Sponsors are required to submit an IND application to FDA prior to initiating clinical research. The IND must include animal study data and toxicity data, manufacturing information, clinical protocols, data from any prior human research, and information about the investigator. The FDA has 30 days to review the original IND submission. Clinical trials are allowed to proceed once the IND is approved by FDA. The FDA may decide a clinical hold to delay or stop the investigation if it is believed that participants are exposed to unreasonable or significant risks, investigators are not qualified, materials for the volunteer participants are misleading, or the application does not include sufficient information about the trial's risks.

The formal regulations that pertain to INDs can be found in Section 21 of the Code of Federal Regulations [15]. There are several parts referring to INDs, including the following: drug labeling, orphan drugs, protection of human subjects, financial disclosure by clinical investigators, IRBs, and GLPs for nonclinical lab animal studies.

5.3 Clinical Development Phase

Once FDA approves the IND, a drug candidate can move forward to human clinical trials. CDER oversees the clinical trials necessary for the FDA to determine whether a new medication will be approved for use. The ultimate goal is to determine the efficacy, safety and quality of drug candidates and ensure the right dose and dosing schedule for a specified patient population. Other desirable properties of drug therapies include good bioavailability with low variability, distribution to the site(s) of action, limited metabolism, and a broad therapeutic index.

The sponsoring company may conduct the early studies with clinical research companies or academic institutions with dedicated facilities for the conduct of early phase research until they reach the later phase larger clinical trials. Pharmaceutical companies often contract with Contract Research Organizations (CROs) to conduct and oversee their clinical trials. The CROs contract with private research clinics, academic research centers, physician groups, and hospitals to conduct the studies in order to enroll the number of patients required. The CROs provide oversite and monitor the sites to assure that they are completing research documentation in an appropriate manner. In this phase, regulatory compliance and oversight is in place and the clinical trials must comply with FDA Good Clinical Practices (GCP) [34]. These regulations are designed to ensure the integrity of clinical data and protect the rights, safety, and welfare of human subjects.

There are three phases of clinical trials, typically starting with a small group of healthy volunteers (Phase I) to determine the safety and basic pharmacokinetics of the test product, to large studies involving hundreds to over one thousand patients at

multiple study sites (Phase III). In order to progress from one phase to the next, the FDA must review the data and decide whether to allow the studies to progress to the next phase. This is considered "IND maintenance."

Clinical trials are designed to establish the efficacy and safety of investigational drug products and to answer other questions about the agent as needed. Protocols are developed that explain what will occur in the trial, how it will be conducted, and why each step is necessary for answering scientific questions about the product as well as safeguarding the health of participants. The trials must follow the study plan that is developed by the researcher or manufacturer and approved by the FDA. Trial participants must meet the eligibility criteria defined in the protocol in order to qualify, and the plan stipulates how many people will participate in the study and how long it will last. The research questions and objectives will dictate whether the trial will include a control group, how the drug will be administered, what dose(s) will be studied, as well as how the data will be reviewed and analyzed.

5.3.1 Phase I Clinical Trials

Traditionally, Phase I psychotropic clinical trials have focused on pharmacokinetics (PK), safety, tolerability, and definition of the maximum tolerated dose. The PK profile is impacted by the drug's physicochemical properties, formulation, and route of administration. In addition, extrinsic factors including diseases, other medications, and food can impact the PK profile, and traditionally only healthy male volunteers have been included as research subjects in psychotropic Phase I trials. The clinical pharmacology information from Phase 1 informs the design of Phase II and III trials.

More recently, individuals with the disease state of interest are being incorporated into Phase I studies. For example, it is known that individuals with schizophrenia tolerate D2/D3 antagonists better than healthy individuals. Studying subjects with the target illness in Phase I studies may better predict the dosages to be used in Phase II trials [23]. In addition, psychotropics have significant adverse effects, and medications with the potential for use in difficult-to-treat mental illnesses may have Phase I trials conducted in the population that would receive the medication. An example is clozapine. After clozapine was found to cause agranulocytosis, its bioavailability study for the NDA for use in treatment-resistant schizophrenia was shifted to be conducted in males with treatment resistant schizophrenia [13].

Phase I studies may be either open label or randomized, placebo-controlled, double-blind trials, escalating single and multiple-dose studies in a small number (12 to 100) of healthy volunteers. There may be two phases to these studies: a single ascending dose (SAD) phase and a multiple ascending dose (MAD) phase; the SAD phase is conducted first, followed by the MAD phase.

There has been increasing interest in collecting pharmacodynamic data as part of Phase 1 trials with the hope of informing the design of Phase II trials, particularly as it relates to dose. Increasingly, potential biomarkers are being introduced into

early clinical trials. In order to be useful as an outcomes measure in clinical trials, the biomarker needs to confirm the diagnosis or predict response to treatment. For example, it has been suggested to perform targeted neuroimaging and collection of potential biomarkers during Phase I [56]. The effects of drugs on neural circuits can be studied using such techniques as function magnetic resonance imaging 9fMRI) and high-density electroencephalography [37]. The use of cognitive challenges during fMRI in individuals with schizophrenia may allow for the identification of medications with pro-cognitive effects.

Mismatch negativity (MMN) has been described as possessing nearly all of the features of a translational research biomarker. It is a neurophysiological response usually measured by auditory evoked potentials that involve assessing the effects of an uncommon stimulus that follows repeated normal stimuli. It is impaired in schizophrenia and involves both dysfunction in neural circuits and clinical outcome. Dysfunction in schizophrenia involves impairment in both auditory sensory perception and cognition. It can be used in both rodents and humans, and NMDA receptor antagonists such as ketamine or phencyclidine negatively affect it in both preclinical and clinical models. Both glycine and the glycine agonist D-serine reverse the negative effects of ketamine on auditory evoked potential [8].

In perhaps the best example of the use of a biomarker in antidepressant studies, the effects of deep learning on the fMRI was associated with an R^2 of 0.48 on predicting Hamilton Depression Rating Scale (HAMD) improvement with a number needed to treat (NTT) of 4.86 patients [57]. It has also been suggested that the use of fMRI during Phase I trials could actually decrease the overall cost of drug development. Another example is the use of positron emission tomography (PET) to study molecular interactions and potentially determine the dosages associated with efficacy or adverse effects.

Currently marketed antidepressants cause neurogenesis in the hippocampus. MRI measured changes in hippocampal volume have been proposed as a screen for potential antidepressant effect. If increases in hippocampal volume predict antidepressant activity, this could be used to explore the potential of compounds not acting on monoamine receptors as antidepressants. This technique is also appealing because it can be used in both humans and nonhuman species. Although this has been explored in a Phase 1b clinical trial, it is too early to confirm its predictability [25].

Thus, the use of multiple pharmacodynamic measures during Phase I studies may help identify unique mechanisms and the clinical profile as well as to better predict the dosages to use in Phase II trials, and perhaps even efficacy [23]. However, there is a need for harmonization and standardization of the methods used. If biomarkers that predict a drug's efficacy can be developed, these could be used in Phase I clinical trials in patients with the disease of interest. If no positive effect on the biomarker is found, then costly Phase II and Phase III clinical trials could be avoided. Although not yet definitive, brain-derived neurotrophic factor (BDNF) is potentially such a biomarker for antidepressant activity [73].

Increased use of Model Informed Drug Development (MIDD) is guiding clinical trial development, optimizing dosing, and providing supportive evidence for

efficacy and in policy development. The use of modeling has the potential to speed up the development process and increase efficiency of conducting clinical trials to support drug approval. Extrapolation of efficacy and safety from small data sets in difficult-to-study populations (children, rare diseases, hepatic dysfunction, drug interactions etc.) and making model-based inferences in lieu of pivotal clinical data to make efficacy, dosing, and safety recommendations are two high impact areas for use of modeling in drug development. Population pharmacokinetic computer modeling (in silico) in CNS drug development is increasingly being used, especially in the area of dose formulation [43, 75]. The FDA and EMA have developed several guidance documents for modeling in the drug approval process. [24, 26, 36, 67].

The importance of early pharmacodynamic studies is clearly recognized. Assessing "pharmacodynamic target-based measures" early in clinical research may not only help dose response relationships to be used in Phase II and III trials; it potentially helps better define mechanism of action. The NIMH through its contracting process has created research teams comprised of pharma researchers, academics, and NIMH researchers to support early pharmacodynamic assessment of candidate agents [41].

FDA reviews the Phase I data and if they find sufficient evidence to support continuing clinical trials, the drug candidate is allowed to move into Phase II. Phase I studies typically last several months, and 70% of drugs move to the next clinical phase [29].

5.3.2 Phase II Clinical Trials

Phase II studies focus on the drug's efficacy and adverse effects. They can last from several months to 2 years in duration. Phase II trials involve testing the experimental drug on a larger number (up to several hundred) patients who have the disease of interest. Phase II trials are dose finding studies looking for the appropriate doses for evaluating safety and efficacy in larger Phase III trials. These trials generally include a study arm which uses up to the maximum tolerated dose (MTD) from the Phase I trials. Because of the small number of subjects in Phase I, the dose may need to be adjusted either down if excessive toxicity is observed or increased if the desired biological effect is not seen.

Early Phase II trials are often open label, but randomized placebo-controlled trials are required by the FDA to demonstrate efficacy. Because of the large placebo response rates seen in most studies of mental disorders, a placebo group must be included to prove efficacy. The FDA does not allow the use of standardized treatment comparison studies (i.e., noninferiority trials) without a placebo group [29].

It is critical that a priori sample sizes be calculated to assure that adequate number of subjects are enrolled to be able to show a statistical difference between groups. Conventionally, an $\alpha \leq 0.05$ is used to demonstrate a difference between groups. Although β may vary, it is typically $\beta \leq 0.2$.

It is essential to assure that patients enrolled into clinical trials have the disorder of interest, and the Structured Clinical Interview for DSM (SCID) or MINI International Neuropsychiatric Interview (MINI) are generally required to verify the patient's diagnosis. In general, patients with varying duration of illness or numbers of episodes are included in Phase II and III trials. However, if an indication for a treatment resistant disorder is being sought, then the patient subject population must reflect the intended indication. In some cases, an indication as an adjunctive agent is being sought, then the patient population would be comprised of individuals who failed to obtain adequate response with a standard treatment, and patients are randomized to receive either the investigational drug or placebo plus the standard treatment.

Psychiatric diagnoses are based on a clinical syndrome which is represented by a set of symptoms or behaviors, severity of symptoms, duration of symptoms, impairment in psychosocial functioning, and other clinical characteristics. Symptom overlap occurs from syndrome to syndrome (e.g., anxiety is often present in depression, bipolar disorder, and schizophrenia, as well as in anxiety disorders). Because of the spectrum of symptoms and the overlap, it is challenging to tie any one syndrome to a specific neural circuit. However, it is often possible to tie one specific symptom to a given neurocircuit, and with the correct biomarkers, perhaps to a specific dysfunction in that circuit. Preskorn argues that clinical drug trials should be based upon treating specific symptoms that are associated with dysfunction in a specific neural circuit [64]. Research Domain Criteria (RDoc), established by the NIMH, is an attempt to integrate scientific data with clinical phenomena. This transdiagnostic approach incorporates such data as biomarkers, genetics, neurocircuitry, imagining, and neuropsychology with five domains of human emotion and behavior [21, 64]. Human behavior is divided into five categories based upon positive or negative valence. This has been referred to as a "systems neuroscience approach" to drug development with the goal of understanding the basic neuroscience associated with human behavior [73]. Collection and compilation of these types of data into large datasets may allow for computational modeling of future new medication [21].

Approximately 33% of drug candidates in Phase II trials move into Phase III studies [29]. Use of a different approach to elucidating the clinical effects of potential drug therapies has the potential to improve the percentage of drugs moving into Phase III testing.

5.3.3 Phase III Clinical Trials

Following FDA review and approval of Phase II trial data, sponsors are allowed to continue into Phase III clinical trials. Study participants who have the disease or condition are enrolled and can involve hundreds to a few thousand volunteers. A priori power analysis calculations are performed in order to determine the number of research subjects that must be enrolled in order to evaluate efficacy. However, much larger numbers of individuals treated with the investigational drug are needed

to determine safety. These studies focus on efficacy and monitoring of adverse reactions, dose-response, wider populations, efficacy at various stages of disease, and use in combination with other agents. These large and extensive trials take significant time and are expensive. Increasingly, quality of life and social functioning assessments are being incorporated into Phase III trials.

In the USA, Phase III trials are double-blind and typically placebo-controlled. This helps to eliminate bias when interpreting results. Patients enrolled in Phase III trials are typically between 18 and 64 years of age, do not have a history of nonresponse to psychotropic treatment, have no serious general medical disorders and no co-occurring mental disorders, including alcohol or substance abuse. This "clean" clinical trial patient population is different than that often seen by clinicians in practice, and thus, generalizability of clinical trial results can be limited [51].

Phase III trials are the final clinical phase of test before the drug product's details and clinical trial results are submitted to the FDA for consideration of approval. They generate important data that reflect the test product's efficacy and adverse reactions.

In general, the FDA requires two placebo-controlled, randomized clinical trials indicating that the psychotropic medication is efficacious and safe. If the medication is already FDA approved for use in adults, then only one efficacy and safety trial is required for the same indication in children or adolescents. There are exceptions to the use of the investigational drug compared with only a placebo control group. For example, in the esketamine clinical trials, patients were randomized to receive either esketamine or placebo added to a newly started antidepressant [40]. In Kane's classic study of clozapine in treatment-resistant schizophrenia, chlorpromazine plus benztropine was used as the control [50].

In addition to large randomized placebo-controlled trials to demonstrate efficacy, tolerability, and safety in treating the acute phase of a mental disorder, the FDA requires continuation studies. Since most mental disorders are either chronic (e.g., schizophrenia) or recurring (e.g., major depressive disorder [MDD]), continuation trials must be of sufficient duration for the specific disorder to demonstrate that the drug has continued efficacy and that it is safe and well tolerated. The design of such trials is variable. They may enroll drug responders, and then after the designated continuation phase, patients may be randomized to continue on the investigational agent or receive placebo. This allows comparison of relapse rates following discontinuation [29]. These studies may be performed in either Phase III or IV.

In general, the FDA has required efficacy of psychotropics to be demonstrated by two independent clinical measures, typically both a validated rating scale for the disorder [e.g., Positive and Negative Symptom Scale (PANSS) for schizophrenia and the HAMD for MDD] and a clinical global impression (CGI) scale. The CGI-Severity (CGI-S) is preferred because it is subject to less recall bias than the CGI-Improvement (CGI-I) [29]. Although multiple measures of clinical outcome may be used in a clinical trial, it is critical that the primary measures of efficacy be determined when the trial is designed, or in an a priori fashion. Primary outcomes must show statistical significance (typically $\alpha \leq 0.05$), between active compound and placebo to demonstrate efficacy of the test drug. Efficacy cannot be determined

based upon statistically significant improvements in secondary measures if a statistically significant difference is not found in the primary outcome measure.

Although there is great interest in biomarkers, no universally accepted biomarkers for drug efficacy in mental disorders currently exist. For example, in Alzheimer's dementia, which is often considered both a neurological and a psychiatric disorder, B-amyloid plaques are associated with both the diagnosis and the severity of Alzheimer's dementia. Several anti-β-amyloid monoclonal antibodies have been developed that decrease β-amyloid plaques in the brain, but they have not been shown to improve clinical symptoms or slow clinical deterioration. The Food and Drug Administration's (FDA's) approval of aducanumab is an example of a drug that produced great controversy regarding the use of a biomarker to demonstrate efficacy in Alzheimer's disease. In clinical trials, aducanumab decreased B-amyloid plaques in the brains of patients with Alzheimer's, but it did not consistently improve clinical symptoms or delay cognitive decline compared with placebo [66].

It could be useful to utilize biomarkers to exclude patients from clinical trials who are unlikely to respond to treatment. For example, elevated baseline C-reactive protein (CRP) (> 1 mg/L), a marker of inflammation, has been shown to predict poor response to SSRIs in females, but not in males. It could be useful to use this as a biomarker to exclude women with depression from clinical trials with serotonergic antidepressants. It also appears that patients with elevated CRP serum concentrations respond better with noradrenergic and dopaminergic antidepressants [48, 49].

Challenges exist with the use of rating scales to evaluate efficacy in clinical trials. The total score is the sum of the severity ratings on individual items. The data are not continuous, and ideally, should not be evaluated using parametric statistics. There is not necessarily a linear relationship between change in the total score and the actual clinical status of the patient. For example, depending on the severity of the individual items, a patient with schizophrenia and a PANSS score of 48 could actually be just as or more psychotic than a patient with a PANSS score of 90 [64].

Adaptive design trials have been recommended as one way of improving the demonstration of efficacy. In adaptive designs, prospectively planned interim analyses are performed and the trial adapted without damaging the scientific integrity of the study [56, 69]. This can allow for enrichment of treatment responsive patient populations and may actually decrease the enrollment requirements and allow an earlier decision to be made about success or failure [69].

Placebo response is a huge challenge in clinical psychopharmacology. Placebo response has increased over the past 40–50 years, and in some studies 50% or more of patients have experienced clinically significant improvement with placebo. High placebo response rates can make it challenging to distinguish active medication from placebo. Several reasons have been proposed for the increase in placebo response including: the move by the industry to conduct clinical trials in private clinics rather than academic settings, varying research experience of clinical investigators, the rise of professional subjects who repeatedly enroll in clinical trials, variable intra-rater and inter-rater reliability in performing psychometric assessments, and lack of rigor of clinical investigators in adhering to study enrollment

criteria [51, 56]. In addition, the amount of time that clinical investigators and their staff spend with clinical research subjects at frequent visits potentially serves as a form of supportive psychotherapy. Although it is important to collect appropriate data for efficacy and safety purposes, perhaps data collection should be streamlined in order to shorten the visits. A placebo run-in period, with placebo responders eliminated before randomization, has been frequently used in attempt to decrease placebo response rates. However, a recent large meta-analysis of antidepressant clinical trials found that the use of a placebo run-in did not alter the difference between active drug and placebo response rates [68].

Approximately 25–30% of drugs complete Phase 3 trials and move forward to be considered by the FDA for marketing approval and continuation to Phase IV studies.

5.3.4 Pediatric Considerations

Additional considerations must be given when conducting clinical trials of psychotropic medications in children or adolescents. Obviously, the agent must be used in clinical trials for a mental disorder seen in pediatric populations. A valid scientific rationale must exist for studying the agent in children and the possibility of different pharmacodynamics and pharmacokinetics must be considered.

Both physiological and emotional development are dynamic processes, and potential differences in efficacy and tolerability must be studied for each age group to be included in the FDA product labeling. Juvenile animal studies may also be needed to examine the effects of the agent on growth and development [29]. Medications may have developmentally dependent adverse effects that are different than those seen in adults, and it is important that this be systematically assessed. Currently, no standardized assessments for adverse events in children are required [14]. The three approaches to soliciting adverse effects are general inquiry, checklist of adverse effects previously reported with this drug class, and a systematic potential adverse effects checklist of a review of systems [14]. The limitations of not using a standardized approach to safety assessment challenge became readily apparent in the FDA's assessment of potential suicidality of antidepressants in children and adolescents [63]. Although there is a suicidality item on most depression rating scales, suicidality in antidepressant trials had been primarily assessed by general inquiry. This would result in the clinical investigator recording a narrative note regarding reports of suicidal ideation or attempt. When the FDA saw a potential signal of suicidality in antidepressant trials in children and adolescents, they contracted with an independent group of suicidality experts to blindly evaluate the case reports. They developed a standardized assessment of the case reports, the Columbia Classification Algorithm of Suicide Assessment (C-CASA). After blindly reviewing the case reports, the panel found that the pharmaceutical companies tended to over identify cases as suicide attempts and under identify overall suicidality. This led the FDA to require the use of the C-CASA in evaluating case reports of possible suicidality [63]. In addition, the FDA recommends the prospective use of the

Columbia Suicide Severity Rating Scale (CSSRS) in clinical trials of antidepressants [62, 63].

The clinical failure rate of psychotropic medication is higher in children and adolescents than in adults. There are likely multiple reasons for this. Youth studies share the challenges of high placebo response rates and the limitations of symptom-based assessments of efficacy which are also a bane for psychotropic studies in adults. Placebo response may be larger in children because of parent or other caregiver's expectations for improvement. Children and adolescents tend to have significant state dependency with regard to symptoms such as depression and anxiety, and thus, spontaneous improvement may occur depending on the youth's environmental situation. Studies in children and adolescents commonly include a broad age range. CNS as well as other organ development is a dynamic process throughout childhood, and including broad age ranges introduces greater heterogeneity into the subject population. The sample sizes in these studies are typically too small to perform subgroup analyses [40].

5.4 Regulatory Review Process

The FDA ensures that US consumers have access to safe medicines and treatments. The FDA's CDER evaluates new drugs before they are approved to be marketed and sold [33]. The regulations that CDER enforces ensure that drug products are safe and effective and that their benefits outweigh any known risks. There are mechanisms in place, including labeling, dosing directions, patient package inserts, and other education materials, to ensure that healthcare professionals and patients have the information they need to use medicines appropriately.

CDER teams composed of clinicians, chemists, statisticians, pharmacologists, and other scientists to review the sponsor's submitted data and make the determination whether there is sufficient proof that the drug should be allowed to move into the next phase in the pathway. These are scientific, unbiased, independent reviews by CDER teams – they review data to assess whether there is sufficient evidence to either approve or reject the company's application to approve a new drug product.

The FDA commonly issues guidance documents to assist sponsors in designing studies that are appropriate for NDA submission. However, these guidance documents often lag behind advances in research in the discipline. For example, the last FDA-approved guidance document for the development of drugs for MDD was approved in 1977. A draft of a revised guidance document for MDD was released for comment in 2018, and it had yet to be approved by submission of this chapter [30].

Because of the pharmaceutical industry's reluctance to perform studies in children, the Congress passed two important pieces of legislation – the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). PREA requires the industry to perform efficacy and safety studies of

certain drug categories in children if the product has the potential to be beneficial for children with the given disorder. The BPCA grants the company an additional 6 months of patent protection if the company conducts studies in children. It is noteworthy that the BPCA also provides the NIH with funds to study drugs FDA approved for use in adults if the medication would be potentially beneficial for children and adolescents [40].

5.4.1 Regulatory Pathway: Clinical Trials to Commercialization

A new drug application (NDA) can be filed with the FDA for review and approval following completion of clinical trials. Throughout the development pathway, efforts to scale up production of the active therapeutic ingredient (ATI) and the final formulation are occurring.

During every development phase, sponsors collect information and data to include in the NDA. These data will need to be sufficient and compelling so that FDA reviewers can determine whether the drug's safety, efficacy, labeling, and manufacturing align with FDA's goal of approving products that meet strict criteria and whose benefits outweigh their risks, ultimately ensuring product quality and integrity.

The NDA document presents a story of the drug's development, from the ingredients in the dosage form to the results of animal testing and stability studies, including results from clinical trials, profiles of drug absorption, distribution, and metabolism, and pharmacodynamics, toxicology, manufacturing and packaging processes, and labeling requirements.

The timeline for reviewing NDAs has been significantly decreased in the past 20 years. The median FDA review and approval times have decreased from 20.9 months and 26.9 months in 1993 to 10.1 months and 10.1 months in 2016 [27].

5.4.2 NDA Review and Approval

The first step in the NDA approval process is for the FDA review team to determine whether the application is complete. If it fails to meet this standard, the review team can refuse to file the NDA. For complete NDA's, the team has 6–10 months to decide if the application meets the standards for approval. In addition to reviewing the various sections, FDA inspectors visit clinical sites to ensure there is no evidence of fabrication, manipulation, or withholding of data. The various reviews and other documents are consolidated into an action package or the formal record of the FDA review.

For drug products shown to be safe and effective for their intended use, the FDA will work with the sponsor company to develop and refine the prescribing,or labeling information. Labeling is a prominent feature that must accurately and objectively describe the basis for approval and the best use for the drug.

It is common for an application to have issues, both major and minor, that need to be resolved prior to approving a drug for marketing. These can range from questions pertaining to existing data to the FDA requiring additional studies. It is up to the sponsor company to decide whether they want to continue development of the product.

5.4.3 Abbreviated NDAs

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as Hatch-Waxman, established the approval pathway for generic drug products and provisions that involve patents and exclusivities related to new drug applications. The approval of generic drug products requires submission of an Abbreviated New Drug Application (ANDA) [32].

These are considered abbreviated since generic drug approvals generally require limited preclinical and clinical data to establish safety and efficacy since they are allowed to refer to the innovator company's data that were submitted in the original NDA. Generic applications must scientifically perform in the same way as the innovator company's drug product. This can be accomplished using in vitro and human in vivo testing to prove that there is bioequivalence – the same rate and extent of absorption, distribution, metabolism, and excretion – when compared with the innovator product.

The FDA has an additional "hybrid" or "bridge" pathway called the 505(b)(2) pathway, for new products that aren't necessarily a copy of the originator product. Examples might include new formulations, new indications, new combinations, new route of administration, minor changes to the molecule such as prodrugs, etc. The application uses all of the safety and efficacy data from the originator product and creates a bridge between their new product and the original product.

5.4.4 Advisory Committees

The FDA has established advisory committees to provide FDA with independent opinions and recommendations from outside experts on applications to market new drugs. These committees are composed of outside experts, who receive a summary of the information from the sponsor application and have access to the FDA's review of the application documents. Advisory committees recommend approval or rejection of an NDA; however, FDA makes the final decision.

5.4.5 Expedited Review Programs

The FDA's expedited review programs are intended to facilitate and expedite development and review of new drugs that address unmet medical needs in the treatment of a serious or life-threatening condition. The four programs are fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. The purpose of the expedited review guidance is to provide a single resource for information on the FDA's policies and procedures for these four programs as well as threshold criteria generally applicable to concluding that a drug is a candidate for these expedited development and review programs. In particular, "breakthrough therapy" designation allows for more rigorous feedback and expedited review than earlier expedited review programs [11, 32, 37].

5.4.6 Prescription Drug Labeling Information

FDA approves labeling information provided to patients in medication guides (MG), patient package inserts (PPI), and instructions for use (IFU). These are available for consumers and patients and include facts about adverse effects, drug interactions, proper storage, and other useful information. These various types of labeling information align with the FDA's Risk Evaluation and Mitigation Strategy (REMS) drug safety program for medicines with serious safety concerns. REMS are created with the goal of ensuring proper use, monitoring, and safe use of medications.

PPIs provide the information that is included in patient labeling, providing comprehensive and considerable detail about a drug product. These are developed by the manufacturer, approved by FDA, and required for specific products or classes of products. For other products, PPIs may be submitted to FDA on a voluntary basis by the manufacturer and approved; however, distribution is not mandated.

MGs are primarily for outpatient prescription products with potential serious public health concerns and are provided to the patient when the product is dispensed. They are required if labeling could help prevent serious adverse events, enhance patient adherence to directions or affect a patient's decision to use a product. IFUs are FDA approved labeling developed by the manufacturer that are dispensed with specified products with complicated dosing instructions. These are intended to help the patient properly use the product.

5.5 Phase IV Activities

FDA oversight continues after a drug product is approved for marketing and is referred to as post-marketing surveillance. Following NDA approval, compliance with manufacturing and distribution of new drug products is closely monitored. During Phase IV,

additional clinical trials may be required for observing long-term efficacy and ongoing monitoring of adverse effects and assessment of health outcomes.

5.5.1 Phase IV Clinical Trials

Phase IV clinical trials may be required of the drug product sponsor as a condition for approving the marketing application. Pre-NDA clinical trials only monitor hundreds to a thousand or more patients while Phase IV trials monitor how a drug product performs in a broader population. These studies aim to assess the long-term risks and benefits, monitor known adverse effects, and identify any rare but serious adverse effects. The Phase IV trials can increase confidence in a product. However, in some instances, the product may be withdrawn from the market based on what is discovered when it is used in larger populations.

Pharmaceutical companies may decide to perform comparative efficacy studies as part of Phase IV. These may be noninferiority or superiority trials. These are often performed in hope of providing the company with a marketing advantage for the drug. The company may decide to pursue additional indications for the drug or obtain FDA approval for the use of the drug in other populations (e.g., children or adolescents), and this results in a return to Phase III trials.

5.5.2 Monitoring Adverse Effects

The FDA has created a post marketing safety surveillance program for all marketed drug products. The regulations require manufacturers to report adverse events received from healthcare professionals and consumers for inclusion in the FDA Adverse Event Reporting System (FAERS). This allows the FDA to identify and monitor new safety concerns, evaluate a manufacturers' compliance with FAERS regulations, and provide information in response to outside requests. Additionally, voluntary reports can come directly from healthcare professionals and consumers. This database allows interested parties to find information regarding adverse events for drug products.

5.5.3 Phase IV Health Outcomes/Quality of Life

Following the approval of a new drug product, the Phase IV trial data may also study other characteristics of the drug therapy, including the impact on a patient's quality of life or the cost effectiveness of the treatment. These questions may take years to answer and are influenced by other factors including the quality of medical care, treatment outcomes, hospital readmissions, the patient experience, and mortality.

5.6 Bioethical Issues

Protection of human subjects should always be at the forefront of designing, implementing, and conducting clinical trials. The FDA [15] and the European Medicines Agency (EMA) have both promulgated rules around human subjects' protection – most of which are very similar in nature and structure with key differences. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has developed guidelines to help navigate these regulations commonly referred to as Good Clinical Practice [47]. Much of the regulations and guidance is derived from key foundational documents – the Nuremberg Code [2], the Belmont report [72], and the updated report from the Declaration of Helsinki [76]. The FDA also has guidance for sponsors, investigators, and institutional review boards. [35].

Each of these outlines the necessary steps for assuring the rights and welfare of human subjects – including the review by institutional review boards, informed consent procedures, the processes involved to mitigate risks to subjects, and clinical trial design expectations with respect to assuring the quality of the work, the feasibility of the study, and the reliability of the results. Study design is a critical component to assuring the ethical construct of a clinical trial. That is, making sure the trial is designed to produce results that are meaningful and reliable and have utility. ICH has developed multiple guidelines for the design and conduct of clinical trials [45].

There is also the issue of people from racial and ethnic minorities being underrepresented in research. Diversity, which includes race, ethnicity, gender, socioeconomic status, age, and stage of disease, is essential to the clinical trial industry to improve the safety and efficacy of new treatments being developed and the generalizability of results. The lack of diversity in clinical trials is an obstacle to understanding the safety and efficacy of novel therapies across population subgroups, which is important for reducing disparities.

Development of drugs for psychiatric conditions has all the same ethical challenges that developing drugs for other conditions would pose. Psychiatric drug development also presents some ethical challenges unique to the conduct of psychotropic clinical trials. Psychiatry and patients with mental illness are subject to higher degrees of stigma, and some individuals are critical of the very nature of the field, leading to a higher level of negative attention from many sources. Patients with mental illness are often perceived as being particularly vulnerable – even to the point where even the notion of conducting trials in the population is questioned. Clearly, there is a need to better understand the biological and physiological underpinnings of psychiatric illnesses and develop a better taxonomy that would facilitate study of more homogeneous subpopulations of patients.

At the forefront of ethical issues in psychiatry is the use of placebos versus active comparator study designs. The double-blind placebo controlled study design has long been considered the gold standard in creating evidence of efficacy in psychiatric clinical trials. Notably, the FDA still provides guidance that the use of placebos is one of the more certain strategies for showing efficacy of a new molecule. The

EMA uses the Declaration of Helsinki as a guide for the drug development process. The Declaration of Helsinki is clear about the use of placebos in clinical trials:

Use of Placebo

"The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: [76]

- Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
- Extreme care must be taken to avoid abuse of this option."

The EMA by in large does not allow placebo-controlled research for psychotropic drug development. The divergence of guidance across the continents is challenging in psychiatry as it is difficult to satisfy both guidance documents when simultaneously developing a drug in Europe and the USA. Unfortunately, the solution is to conduct separate trials to meet the specifications, exposing greater numbers of subjects to potentially nontherapeutic and noxious agents, increasing the cost of drug development, and delaying the development of the products.

The ethical issues surrounding the use/nonuse of placebos are multifaceted. On the surface, the concern would seem to be the use of placebos amounts to withholding treatment in patients with serious disorders for the duration of the trial. For psychiatric disorders, this increases the risk for symptom exacerbation and relapse with potential consequences of suicidal ideation/attempt, death by suicide, reincarceration, and a host of social/educational/employment consequences.

Clearly placebos are unethical when the consequence of withholding standard treatment is lethal or has the potential to cause irreversible morbidity. Placebos are also considered ethical – as guided by the Declaration of Helsinki when there are no standard treatments and, in the situation where the experimental therapy is added to standard therapy. Exploring the issue further, one must ask – what are the alternative study designs to placebo-controlled studies and the ethical consequences of those alternatives?

Active control studies would seem to be the logical alternative – comparing the test compound with currently available treatments. The challenge with this approach in psychiatry is the high rate of placebo response in clinical trials (30% or greater), resulting in a high number of failed studies. The results of active control studies would be challenged on the basis of the reliability of the results and risks approving a therapy that might in actuality be no better than placebo. For example, if a comparator study showed an investigational drug to be equally effective as diazepam in generalized anxiety disorder, one would conclude that the investigational drug is effective. However, if a placebo group was included in this study, and placebo

response was equivalent to the investigational drug and diazepam, then it is a failed study. If a study design produces unreliable results – then the ethics of enrolling subjects into the study comes into question. Furthermore, the active control design would need to use a superiority analysis design – the test compound would need to be better than the standard. Superiority is a high hill to climb in developing drugs for psychiatric conditions that are highly variable along many constructs. Most new agents to market are no more efficacious than existing therapies.

Noninferiority analysis, where the test compound is compared to a standard treatment, is another design to be considered. The question that arises with these analyses is whether the endpoint of noninferiority has any clinical utility – again bringing to question the ethics of enrolling subjects in such a study. Additionally, noninferiority studies often need to have significantly more subjects enrolled in the trial, potentially increasing the exposure to a test product that could have serious adverse effects or may not be efficacious.

Clearly there are good arguments on both sides of the placebo/antiplacebo debate. At this point, the FDA continues to press for "adequate and well-controlled" studies to demonstrate the effectiveness prior to approval. It is likely we will continue to see a mix of randomized placebo-controlled trials (RPCT) and other designs used to meet this standard. When placebos are utilized in a trial, Miller offers four ethical considerations for design and implementation [12, 55]:

1. Placebo-controlled trials must be scientifically sound and the results of the study have potential significant clinical utility.
2. Risks should be minimized and justified relative to the anticipated benefits to clinical care and individual subjects – subject selection should consider risks and benefits to the individual; there should be a plan for managing distress associated with temporary exacerbations and removal of the subject from the trial if severe. Monitoring/assessment should target known risks such as suicidal ideation, and duration of exposure to placebo should be as short as possible.
3. Subjects must give adequate informed consent – free from coercion, with clear delineation that it is research and not treatment, the chances of receiving placebo are understood, and individual vulnerabilities are attended to.
4. Subjects should be offered short-term individualized treatment after completion of research participation to maintain their symptom stabilization and be referred for continuation of care

Another key challenge to clinical trial work in the psychiatric population is the perception that patients are a vulnerable population and therefore must receive higher levels of protection. Vulnerability within the population of people with mental health disorders can be grouped in to two major categories – capacity-based vulnerability and power-based vulnerability. Capacity-based vulnerability refers to the inability to make an informed consent decision based on the subject's impaired capacity. Power-based vulnerability refers to the power differential between the subject and the subject's provider/investigator. There also exists a wide range of vulnerability within this population and not all subjects are considered vulnerable. For example, studies in depression found that 90% of subjects had full

comprehension and that the levels of comprehension were similar to patients from the general community [4, 70]. Clearly there are subgroups within the population that are more at risk for capacity-based vulnerability that need to be identified [78].

The ability to provide voluntary consent often comes into question in trials of psychiatric conditions. Much has been written about the decisional capacity of psychiatric patients in clinical trials. The four key principles of decisional capacity with respect to providing informed consent are understanding – ability to know the meaning of information, appreciation – relating the information to oneself, reasoning – using information to weigh the options, and expressing a clear choice – making a clear decision [5, 42]. There are many different approaches to assessing capacity. The use of the MacArthur Competence Assessment Tools for Clinical Research and for Treatment (MacCAT) is an assessment tool with good empirical data to support use in populations of subjects where the subjects' ability to understand, appreciate, reason, and express a choice are questioned. The MacCAT has been utilized in the consent process to verify decisional capacity [22] L). Additionally, there are considerations, again not unique to psychiatry, surrounding the use of a legal guardian, spouse, parent, or other surrogate to make decisions for the subject who may not be capable of deciding about trial participation.

Including patients in clinical trials that are involuntarily detained is a relatively unique challenge in psychiatry. These are patients admitted to a psychiatric facility under the provision of civil involuntary detention laws – where a clinician and judge are making decisions about treatment. States and local treatment culture vary in how to handle cases where the patient qualifies for enrolling in a clinical trial but is involuntarily detained. The willingness of guardians to allow their wards to participate in clinical trials also varies. Public administrator guardians may be less likely to agree to participation – especially in higher risk studies – and often request judicial review prior to signing the consent form. Family member guardians may also be more protective of their loved one. Interestingly, family members may also be more likely to agree to allow participation under the notion that they are helping the patient find a better treatment – especially if the patient has had difficulty managing symptoms. In any case, there should be an agreement by the subject to participate (assent) if a surrogate is providing consent.

Research subjects and guardians may have higher than reasonable hopes that participation in the clinical trial will provide benefit – so called therapeutic misconception. These misconceptions where the subjects fail to appreciate the differentiation between the requirements and obligations of clinical research and treatment as usual can undermine the potential for the subject to provide a true informed consent.

The perceived benefit can come in many forms – increased attention or potential for improvement in long-standing symptoms. In the minds of patients, these may be prioritized over the weighing of potential risks, disadvantages and incumbrances associated with the study procedures. The therapeutic alliance a provider has with the patient is an important bias that has the potential to increase this misconception as patients may be more likely to follow the recommendation of their provider and the provider, out of an obligation to do what's best for the patient, may be more likely to refer to a clinical trial if it appears to offer a benefit that cannot be currently

provided [6]. Clinical trials designed with randomization, and which use strong informed consent processes that do not involve the provider as the one explaining the study, that make a clear distinction between the objectives of the research, and which acknowledge that research by definition has inherent risks and may not result in the patient deriving any benefit from the study are the ones more likely to be perceived as being ethically designed and implemented. Potential therapeutic benefit to the patient is a secondary issue to consider and discuss with the subject [12].

Another challenge in designing clinical trials is creating a set of experiments that answers pressing clinical issues and the results of which are translatable to clinical practice. Few molecules in development have the potential to revolutionize the practice of psychiatry. Often, drug development clinical trials in psychiatry are directed more toward developing molecules that provide a better tolerability profile or provide some incremental improvement in drug delivery. As such, the inclusion/exclusion criteria are relatively narrow. Subjects with significant medical problems, drug interactions, multiple comorbid psychiatric conditions, suicidal ideation, substance use disorders, and significant social-economic burdens such as homelessness are often excluded from participation. In addition, pediatric and geriatric populations are often not included in clinical trials. Pediatric studies are often included in the additional studies required by the FDA in the post-marketing phase of drug development. Excluding these patients from the trials serves the purpose of creating a set of results that favor the developing drug product but produce results that do not necessarily serve the greater good as the complicated patients that comprise a significant portion of patients in clinical practice are not reflected in the results. [44, 46]

Along these same lines, the US Department of Justice estimates that up to 43% of inmates may have a history of mental illness and up to 40% of inmates are receiving treatment for mental health concerns [74]. In addition, growth in the forensic psychiatric population within the behavioral healthcare system continues to grow. Clinical trials with these populations are fraught with ethical complications, and it is important to remember the IRB regulations regarding the use of prisoners in clinical trials. Notwithstanding the complications of getting informed consent from judges, and the challenges of working with a population with highly complex illnesses, the potential for coercion in this population is high. Clearly, the same standards of treatment for incarcerated subjects should exist as for any other trial participant. Similarly, there should be no special incentives provided such as gaining access to certain privileges or leverage in decisions around parole. Subjects who are incarcerated may be motivated/coerced by perceived incentives – simply spending time outside of the cell or prison milieu may be viewed as an incentive. Clearly monetary incentives are viewed differently in prison relative to the community. A prisoner representative of the IRB must attend the meeting where the study is reviewed [12].

Financial payments for participation are often reviewed with higher levels of scrutiny by IRBs. A perception exists that patients with psychiatric diagnoses, especially those that are unemployed or on disability, may be coerced into participation by smaller amounts of remuneration than the general population. Very little empiric evidence is available to support this notion. However, concern does exist about

providing cash payments to subjects that might be at risk for substance use. But again, there is no evidence to support that providing non-cash payments reduces this risk. IRBs have wide ranging policies and guidance for providing remuneration to vulnerable subjects.

5.7 Conclusions

As evidenced in this chapter, drug development is an expensive, high risk, and long process. Once molecules with potential therapeutic effect are developed, they must have extensive in vitro and animal testing before entering trials in humans. A sequence of studies is conducted in humans to determine the characteristics of the drug in the body and its efficacy and safety. It is a highly regulated process, and ethical considerations are given paramount importance.

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