DRUG DISCOVERY IN NEUROSCIENCE

ABSTRACT

Neuroscience involves the scientific study of the nervous system and this is a major area for disease and consequently disease management. Pharmacotherapy is the main stay of treatment for neurological disorders and this essay will concentrate of the history, process, constraints and novelty of drug discovery with emphasis on three main areas of neuroscience: 1. sedative/hypnotic agents, 2. anti psychotic drugs and drug treatment of neurodegenerative disorders. This will enhance understanding and contribute to an improved efficiency of the drug development process. Drug Discovery in modern times straddles four main periods. The first notable period can be traced to the nineteenth century where the basis of drug discovery relied on the making of unexpected and fortunate discoveries by the medical practitioners. Although substances had been prescribed by physicians and health care practitioner for earlier years, the pharmacology involved in their discovery was largely based on trial and error. These drugs often originated from fungi, herbs, and various other common plants known at the time, but there was little or no scientific knowledge and understanding to why certain substances produced certain results. The second period commenced around the early twentieth century when new drug structures were found, which contributed for a new era of antibiotics discovery. Based on these known structures, and with the development of powerful new techniques such as molecular modelling, combinatorial chemistry, and automated high-throughput screening, rapid advances occurred in drug discovery towards the end of the century. Another period also was

revolutionized by the emergence of recombinant DNA technology, where it became possible to develop potential drugs target candidates. Presently drugs can be designed completely from the laboratory based on known structure / activity relationships and drug mechanism analysis. The success of mechanism-based drug discovery depends on the definition of the drug target. This definition becomes even more important as we try to link drug response to genetic variation, understand stratified clinical efficacy and safety, rationalize the differences between drugs in the same therapeutic class and predict drug utility in patient subgroups.

Keywords: Discovery, Preclinical, Clinical, Pharmacovigilance, Neuroscience

1.0 INTRODUCTION

The history of drug discovery in neuroscience follows the pattern of other discoveries in civilisation. Natural extracts from the natural world were the only source of medicines until experimental procedures were developed to purify active principles from these extracts. Most often, the development of a new medicinal drug starts when scientists learn of a biological target that is involved in a biological process thought to be dysfunctional in patients with a disease such as Alzheimer's disease. Better medicines that are improvements on current medications are further found to be more valuable as they offer benefits over existing medications in terms of potency, safety, tolerability, or convenience. In accordance with this, neurological drugs have lower success rates and take a longer time to develop, than do other drug classes. Specifically, the success rate of neuropsychiatric drug candidates who enter into human testing to effectively reach the marketplace is dramatically lower (8.2%) than for all drugs combined (15%) [1,2] , the average clinical development time for neuropsychiatric drugs is in the order of 8.7 years, as

compared with 5.9 years for antiviral agents, almost 50% longer. The time required to gain regulatory approval is also longer for neurological drugs, 1.9 years as opposed to an average of 1.2 years for all drugs. Taking into account the approximately 6 to 10 years that drugs generally are in the preclinical phase of development, neurological drugs can take up to 18 years to run the gauntlet from initial laboratory evaluation to regulatory approval and use [1,2] . This is a long duration in relation to the current 20-year patent protection rights. The preclinical and later clinical studies needed to determine the pharmacokinetic properties of a proposed drug are extensive [3] and are particularly complex for CNS targets because of the blood-brain barrier [4].

The range of potentially safe and tolerable doses of a molecule must be determined before human testing. Toxicology studies in at least two nonhuman species are usually used to determine a projected safe dose range and to provide information about compound distribution, organ-specific toxicity, and metabolism [5]. These studies should provide information on the emergence of adverse effects as compound dose is increased and provide guidance on compound-specific monitoring that might be needed in early clinical studies. Serious, irreversible adverse effects observed in these studies within some multiples of the projected efficacious doses are likely to prevent further development of the compound.

1.1 NEUROSCIENCE IN HISTORY OF DRUG DISCOVERY

A drug is generally defined as any chemical that interacts with an organism to alter its function. In history, drugs have been sourced as the disease is identified and the sources currently fall into three main categories; natural, semi synthetic and synthetic. Plants, animals and minerals initially contributed the active ingredient for neurological drugs [6]. However, the science of pharmacology emerged in European records by the 15th century with the work of Paracelsus (1493–1541), who mounted a vigorous attack on accepted paradigm of poly pharmacy and

insisted that drugs should undergo critical investigation [7]. At about the end of the 18th and the beginning of the 19th centuries, methods became available to isolate the active principles from crude drugs [7]. One of the first pure active principle came from the poppy plant, an extract (opium) of which has probably been used for it psychoactive effects longer than any other agent—apart from ethanol. For centuries, opium appeared as a standard ingredient in all sorts of medicinal preparations and was extensively used, even though the dangers of addiction were well known [8]. Paracelsus is credited with compounding Laudanum, a 10% opium compound containing 1% morphine, in the 16^{th} century, and in 1803 Fredrich Sertuner obtained the active substance from the poppy plant. He called it morphine after the Greek god of dreams Morpheus. This stimulated the isolation of the active principles of other important medications especially from plant extracts which could then, only be administered orally. The invention of the hypodermic syringe in 1853 enhanced advancement to the injection of active principles directly to the blood stream for faster therapeutic effect.

DRUG DISCOVERY PROCESS

The process of drug discovery is expensive and as a result mostly carried out by major pharmaceutical companies or large research institutions [9]. Generally, drug discovery in neuroscience includes evaluating therapeutic agents suitable for human use, studying the toxicity / safety [10] and elucidating the mechanisms of the drugs [11]. But typically, researchers discover new drugs through:

- Serendipity
- New insights into a disease process that allow researchers to design a product to stop or reverse the effects of the disease.

- Many tests of molecular compounds to find possible beneficial effects against any of a large number of diseases.
- Existing treatments that have unanticipated effects.
- New technologies, such as those that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.

At this stage in the process, thousands of compounds may be potential candidates for development as a medical treatment. After early testing, however, only a small number of compounds look promising and call for further study. Once a promising molecule has been identified, the process of moving from the basic science laboratory to the clinic begins. This translational research involves preclinical and clinical steps whereby researchers conduct experiments to gather information on:

- How it is absorbed, distributed, metabolized, and excreted (Pharmacokinetics).
- Its potential benefits and mechanisms of action (Pharmacodynamics).
- The best dosage.
- The best route of administration (such as by mouth or injection).
- Side effects or adverse events (toxicity).
- How it affects different groups of people (such as by gender, race, or ethnicity) differently.
- How it interacts with other drugs and treatments.
- Its effectiveness as compared with similar drugs.

The preclinical experiments are conducted with animals in the laboratory [12] while the clinical trials are conducted in humans [13].

2.0 PRE CLINICAL STUDIES

Before testing a drug in people, researchers must find out its potential through two main types of preclinical research: In Vitro and in vivo. In vitro experiments are set biological process occurring in an artificial environment outside the living organism. While in vivo techniques are set biological process occurring within a living organism. The goal of a preclinical drug discovery program is to deliver one or more candidate molecules, each of which has sufficient evidence of biologic activity at a target relevant to a disease as well as sufficient safety and drug-like properties so that it can be entered into human testing. The preclinical experimental studies are carried out in set laboratories using animals and conforming to ethical issues [14, 15]. Examples of such experimental studies in neuroscience include the search for Sedative-hypnotic agents, agents for neurodegenerative diseases and anti psychotic drugs.

Sedative-hypnotic agents: Sedatives are drugs that decrease activity and calm the recipient while hypnotics are drugs that produce drowsiness and facilitate the onset and maintenance of a state of sleep. There are several models for the animal experiments for identification of these types of drugs including the “thiopental induced sleep in mice” and the “ketamine induced hypnosis”. In the sleep induction with thiopental, a sub-hypnotic dose of thiopental (60mg; kg) is administered intraperitoneally 30 mins after administration of test substance. The effect is recorded for loss and regain of the righting reflex. Hypnotic time is considered to be the time interval between loss and regain of the righting reflex [16, 17].

Agents for neurodegenerative diseases: neurodegenerative diseases are characterized by progressive degeneration and loss of neuronal pathways that are involved with the regulation of emotion, behaviour and movement of the organism. Two examples are Parkinson disease and Alzheimer disease. Parkinson disease is characterized by tremor at rest, bradykinesia, rigidity and postural instability. Animal models for the study of anti Parkinsonism drugs include the

"stride length of the paw test". This test is used to measure abnormal movement that is analogous to the shuffling gait in patients with Parkinson disease. The foot print is used to measure the stride length of the paw. In this test the fore and hind limbs of the animal are linked with different colours and the stride length is quantified after a walk down a narrow corridor [18, 19].

Animal experiments for anti psychotic agents: Anti psychotic drugs are tranquilizers used to treat a severe mental disorder in which contact with reality is lost or highly distorted conditions, when a calming effect is desired as in schizophrenia and mania. These drugs were initially termed neuroleptics because of their ability to produce neurolepsis – psychomotor slowing, emotional quieting and affective indifference. Psychosis is a mental disorder characterized by abnormal social behaviour with distorted or loss of sense of reality [20]. It is associated with multiple symptoms affecting thoughts, perceptions, emotions and volition which impair the quality of life of the patients. Schizophrenia is a psychotic disorder characterized by a mixture of three main group of symptoms: positive (hallucinations, delusions), negative (anhedonia, emotional quieting, passivity and apathy) and cognitive symptoms [21]. The aetiology of schizophrenia is still being defined but believed to be related to either a hypersensitivity of the dopamine receptor or that the synthesis or release of dopamine in nerve terminals associated with these receptors is increased. Either of these mechanisms led to excessive stimulation of dopamine receptor sites [22]. Some animal models for schizophrenia were developed using drugs that affect the dopaminergic system as an attempt to mimic the positive response [23]. Amphetamine, apomorphine and ketamine are used to induce stereotype behaviour which presents as repetitive, ritualistic and purposeless motor behaviour [24].

Usually, preclinical studies are not very large. However, these studies must provide detailed information on dosing and toxicity levels. After preclinical testing, researchers review their findings and decide whether the drug should be tested in people.

Drug developers must submit an Investigational New Drug (IND) application to a regulatory agency (RA) before beginning clinical research [25]. The regulatory agency varies from country to country but often follows the same standard pattern. In the IND application, developers must include:

- Animal study data and toxicity (side effects that cause great harm) data
- Manufacturing information
- Clinical protocols (study plans) for studies to be conducted
- Data from any prior human research
- Information about the investigator

Approval

If a drug developer has evidence from its early tests and preclinical research that a drug is safe and effective for its intended use, the company can file an application to proceed with clinical trials [26]. The regulatory agency (RA) review team thoroughly examines all submitted data on the drug and makes a decision to approve or not to approve it. This review team has a specified number of days to review the original submission. The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials. This agency often responds to IND applications in one of two ways:

i. Approval to begin clinical trials.

ii. Clinical hold to delay or stop the investigation. Clinical hold can be placed for specific reasons, including:
    - Participants are exposed to unreasonable or significant risk.
    - Investigators are not qualified.
    - Materials for the volunteer participants are misleading.
    - The application does not include enough information about the trial's risks.

3.0 CLINICAL TRIALS

The clinical trials involve an elucidation of the drug effects on living human beings. This involves an evaluation of the efficacy, potency, pharmacokinetic, pharmacodynamic and most importantly the safety of the drug among other things. An idea of these effects have been obtained from the preclinical stage if it produces the desired effect; but though the human genome is related to that of animals [27], the degrees of variability by size and genetic makeup produces variations in reaction to and interaction with drugs [27]. While preclinical research answers basic questions about a drug's safety, it is not a substitute for studies of ways the drug will interact with the human body. As the developers design the clinical study, they will consider what they want to accomplish for each of the different Clinical Research Phases and begin the Investigational New Drug Process (IND), a process they must go through before clinical research begins [26].

3.1 **Clinical Trials Design**

Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a specific protocol that is developed by the researcher. Before a

clinical trial begins, researchers review prior information about the drug to develop research questions and objectives. Then, they decide:

- What is the selection criteria
- What number of persons are required for the study
- How long will the study last
- Will there be a control group
- what other ways are there to limit research bias
- How the drug will be given to patients and at what dosage
- What are the clinical endpoints for data collection
- How will the data be reviewed and analyzed

3.2 Clinical Research Phase Studies

Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 and 4 studies.

Phase 1

Phase 1 involves the use of very low doses of the drug and closely monitoring of the patients for minimal side effects. A small number of people are used. It is usually done using one treatment outcome e.g. drugs for treating Parkinsonism, using patients with Parkinson disease. The study participants are usually about 20 to 100 healthy volunteers or people with the disease/condition. The study duration is several months and the purpose is to determine the safety and dosage. Approximately 70% of drugs move to the next phase [28].

Phase 2

In phase 2 about 25-100 patients are used with the same disease condition using the method set up in Phase 1. In this phase all study participants get the same dose. It is done in major hospitals while observing side effects and reporting adequately. The study duration is several months to two years and the purpose is to determine the efficacy and side effects. Approximately 33% of drugs move to the next phase [28]

Phase 3

Phase 3 studies are carried out in several clinical centres at the same time after treatments that have been shown to work in phase 2 studies. A large number of patients (250 – 3000 patients) are involved and these studies last longer than phase 1 and 2 studies (1 to 4 years). Patients are monitored closely for efficacy and side effects which could lead to discontinuation of treatment. Positive outcomes in this phase often lead to recommendation for approval. Approximately 25-30% of drugs move to the next phase [28].

Phase 4

Post-marketing surveillance studies

After the three phases of clinical testing and after the treatment has been approved for marketing, there a continuation of monitoring of efficacy and side-effects for a longer period of time in actual conditions after the drug has been approved for use. Such trials are described as pharmacovigilance. They are not necessary for marketing permission.

New Drug Application

A New Drug Application (NDA) tells the full story of a drug. Its purpose is to demonstrate that a drug is safe and effective for its intended use in the population studied.

A drug developer must include everything about a drug—from preclinical data to Phase 3 trial data—in an NDA. Developers must include reports on all studies, data, and analyses. Along with clinical results, developers must include:

- Proposed labelling
- Safety updates
- Drug abuse information
- Patent information
- Any data from all studies that may have been conducted
- Institutional review board compliance information
- Directions for use

4.0 REGULATORY REVIEW

If a drug developer has evidence from its early tests and preclinical and clinical research that a drug is safe and effective for its intended use, the company can file an application to market the drug. The RA review team thoroughly examines all submitted data on the drug and makes a decision to approve or not to approve it. Once the regulatory agency (RA) receives a new drug application, the review team decides if it is complete. If it is not complete, the review team can refuse to file the new drug application (NDA). If it is complete, the review team then make a decision on whether to approve the drug.

In cases where the RA determines that a drug has been shown to be safe and effective for its intended use, it is then necessary to work with the applicant to develop and refine prescribing information with comprehensive and comprehensible labelling [28]. Labelling accurately and objectively describes the quality and use for the drug. If there more issues that need to be

resolved before the drug can be approved for marketing the RA may either require the developer to address questions based on existing data or request for additional studies [28]. Despite the rigorous steps in the process of drug development it may not be possible to have complete information about the safety of a drug at the time of approval. Therefore, the true picture of a product's safety actually evolves over the months and even years that make up a product's lifetime in the marketplace. The RA reviews every report of problems with prescription and over-the-counter drugs, and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues over time [28].

4.1 Supplemental Applications

Developers must file a supplemental application if they wish to make any significant changes from the original NDA. Generally, any changes in formulation, labelling, or dosage strength must be approved by RA before they can be made.

4.2 INDs for Marketed Drugs

If sponsors want to further develop an approved drug for a new use, dosage strength, new form, or different form (such as an injectable or oral liquid, as opposed to tablet form), or if they want to conduct other clinical research or a post-market safety study, they would do so under an IND.

4.3 Drug Advertising

The RA regulates prescription drug advertisements and promotional labelling. By law, a developer is prohibited from advertising unapproved uses of their product. All advertisements, such as product claims cannot be false or misleading. They must contain truthful information about a drug's effectiveness, side effects, and prescribing information. These advertisements can

be found in medical journals, newspapers, and magazines, and on the Internet, television, or radio. Promotional labelling differs from drug advertisements in the way it is distributed.

4.4 Bio-equivalence studies

New drugs are patent protected when they are approved for marketing. This means that only the sponsor has the right to market the drug exclusively. Once the patent expires, other drug manufacturers can develop the drug, which will be known as a generic version of the drug. Generic drugs are comparable to brand name drugs and must have the same dosage form, strength, safety, quality, performance characteristics and intended use. Because generic drugs are comparable to drugs already on the market, generic drug manufacturers do not have to conduct clinical trials to demonstrate that their product is safe and effective. Instead, they conduct bio-equivalence studies and file an Abbreviated New Drug Application (ANDA).

MODERN DRUG PROCESSES IN NEUROSCIENCE

Nowadays the most common source of drugs used in neuroscience is chemical synthesis from rational design of new molecules; other sources include screening for biological activity in large numbers of natural products and chemical modification of a known active molecule. Thousands of compounds undergo the early stages of the process, but very few achieve drug status. Successful candidates have to fulfil the essential criteria of potency, selectivity, bio-availability, therapeutic efficacy and acceptable side effect profile. In recent years, a number of novel approaches for obtaining clinical drug disposition information have been adopted including, microdose and microtracer approaches [29, 30] and the identification and quantification of

metabolites in samples from classical human PK studies using technologies suitable for non-radiolabelled drug molecules [31].

5.0 NAMING OF DRUGS

A substance that becomes officially approved as drug may have at least five different names; a chemical name (indicating the drugs chemical structure), code name (assigned by a manufacturer to an experimental chemical which shows a potential as a drug), generic name (the name assigned by the drug council when the chemical appears to have therapeutic use and the manufacturer wishes to market the drug), official name (the name maintained when an experimental drug becomes fully approved for general use) and brand name (a proprietary name given by a particular manufacturer) [32]. Thus acetaminophen, paracetamol and panadol all refer to the same N- amino para phenol.

6.0 CONSTRAINTS OF DRUG DISCOVERY IN NEUROSCIENCE

Drug discovery in neuroscience is associated with significant challenges: it takes longer to get neuro-drugs to market (12–16 years) compared with a non-neurological drugs-10 –12 years [33]. This is attributable to a variety of factors, including the complexity of the brain, the liability of neuro-drugs to cause central nervous system side effects, the requirement of these drugs to cross the blood-brain barrier, new approaches in animal models of disease and paucity of research infrastructure and resources.

A drug needs to be transported from the site of administration into the systemic circulation and is only considered to be absorbed once it has entered the blood capillaries. The central nervous system is functionally divided into two components- the brain and the spinal cord. One of the most important features of the brain and spinal cord is that they are separated from the blood by the BBB and the blood-spinal cord barrier [33]. These barriers of CNS act as a selectively

permeable membrane and do not completely block all of the incoming compounds [34]. The primary function of the BBB is to make sure that there exists a suitable environment for the interaction and functioning of the neurons, which is important for maintaining homeostasis, regulating efflux and influx and protecting the brain from pathogenic agents [33]. The BBB is formed by a complex network of endothelial cells, astroglia, pericytes, perivascular macrophages, and a basal lamina. Most organs of the body are perfused by capillaries lined with endothelial cells that have small pores to allow for the rapid movement of small molecules into the organ interstitial fluid from the circulation [34 and 35]. However, the capillary endothelium of the brain and spinal cord lack these pores because the endothelial cells of brain capillary are sealed together by continuous tight junctions, produced by the interaction of several trans-membrane proteins that project into and seal the paracellular pathway [36]. The interaction of these junctional proteins effectively blocks the free diffusion of polar solutes from blood along these potential paracellular pathways and so denies access to brain interstitial fluid. Thus, the BBB significantly impedes entry from blood to brain of virtually all molecules, except those that are small and lipophilic or those that enters the brain through an active transport mechanism, particularly with essential nutrients, precursors, and co factors.

A classic example of drug treatment that is made difficult by the blood-brain barrier is that for Parkinsonism, a disease involving poor motor coordination and regulation. It was found that there is a brain deficiency of dopamine in patients with Parkinsonism. Therefore it should be possible to give such patients dosages of dopamine and cure their ailment. Unfortunately dopamine will not cross the blood-brain barrier, even if injected directly into the blood stream. However the chemical precursor of dopamine, which is laevo dopa, is absorbed across the blood-brain barrier by active transport, and once in the brain, it is transformed into dopamine and helps

regulate motor coordination. Laevo dopa has been successful in the treatment of Parkinsonism because it is able to cross the blood-brain barrier and reach the intended site of action.

Another challenge of drug discovery in neuroscience is the presentation of side effects and this is exemplified with anti psychotic drugs. The neuroleptics produce some of their effects by blocking dopamine receptor sites in the limbic system but dopamine is also found as a neurotransmitter in other areas of the brain such as the basal ganglia, the chemo-receptor trigger zone of the medulla and the hypothalamus. Blockade of the dopamine receptors in the basal ganglia results in extra-pyramidal symptoms, such as; akathisia, tremors, acute dystonia and Parkinsonism [37 and 38]. Blockade of dopamine receptors in the chemo-receptor trigger zone results in an anti emetic effect while blockade of the hypothalamus dopamine receptors result in a decrease in the release of the pituitary hormones such as growth hormone[39]. The neuroleptics also block cholinergic receptor sites producing tachycardia, dry mouth, blurred vision, constipation, urinary retention and decreased respiratory secretions. They block alpha adrenergic receptor sites producing orthostatic hypotension and reflexive tachycardia. These drugs produce some dose related CNS depression leading to sedation, ataxia, respiratory depression and cardiovascular collapse at high doses [40].

Many animal models are based on an increased understanding of human genetics; however, these genetic models present many challenges. Among these challenges are the observations that individual genes and variants may have only small effects and may not be fully penetrant. In addition, large-effect variants often cause constellations of symptoms, which further complicate interpretation; strong-effect risk factors may not be shared across species. The genetic background of the animal can complicate interpretation of phenotypes.

For some nervous system disorders, existing animal models do not produce the key pathologic features or symptoms of the disease, and as a result may not be able to demonstrate whether a drug is going to be effective. For highly heterogeneous diseases such as schizophrenia, there will never be one single model, but several models for specific aspects or subtypes of the disease. Disease modelling is further complicated by the fact that there are aspects of the human nervous system that are not represented in virtually any other animal.

There is insufficient infrastructure and inadequacy of workforce training for neuroscience research coupled with the lack of trained clinicians working at the preclinical–experimental medicine interface to better enable translation of preclinical findings to clinical studies [41]. The challenge of paucity of novel neuropsychiatric drugs can be bridged by addressing them with the following recommendations for potential solutions. First, we need to drive discovery efforts based on human data. Second, we need to think more carefully about animal models, embracing them as tools to test pathophysiological alterations. Third, we need to develop strategies to select more homogenous groups of patients in our clinical trials. Fourth, we need to develop and validate translational biomarkers, which can be used for pharmacodynamic assessments as well as for patient selection. Fifth, we need to adopt more reliable and objective measures to capture clinical efficacy [42]. Finally more funding should be channelled towards improved infrastructure and workforce training for neuroscience research.

CONCLUSION

Drug discovery in neuroscience is both exciting and challenging. From the excitement of discovery of an active principle to the challenges posed by side effects and the blood-brain barrier. Active principles were initially extracted from natural sources but rational drug design is

producing millions of drug candidates on a daily basis. An approved drug maintains nomenclature determined by among other things; the active principle and the manufacturer.

This translational research moves from the ethical use of animals in the laboratories to the clinical trials which continue with pharmacovigilance is impeded by poor infrastructure and trained personnel and can be propagated with improved funding for infrastructure and workforce training.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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