

## **An Appraisal of the Drug Discovery Process in Neuroscience**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

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## **ABSTRACT**

The scientific study of the nervous system is a major area for disease and consequently disease management. The use of drugs to treat neurological disease is the backbone of this sphere of therapy. This review will concentrate of the history, process, constraints and novelty of drug discovery for these disorders. It will enhance understanding and contribute to an improved efficiency of the drug development process. The history of drug discovery in neuroscience follows the pattern of other discoveries in civilisation. Solutions obtained by steeping or soaking natural substances comprised the only source of medicines until data-based processes were developed to; remove impurities from, increase the concentration of, and separate active substances from these extracts. In most cases, the development of a new medicinal drug starts when scientists learn of a target that is involved in a natural process thought to be impaired in function for patients with sicknesses such as Alzheimer's disease. Better medicines that are improvements on current medications are further found to have greater value as they offer benefits over existing ones for disease treatment, prevention or alleviation in terms of potency, safety, tolerability, or convenience. Regulatory agencies are set up to ensure conformity to steps and standards for improved safety and efficacy. In accordance with this, neurological drugs have less success rates and take more time to acquire, than do other drug classes.

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## ABBREVIATIONS

*NDA* : *New Drug Application;*  
*ANDA* : *Abbreviated New Drug Application;*  
*RA* : *Regulatory Agency;*  
*IND* : *Investigational New Drug;*  
*BBB* : *Blood Brain Barrier;*  
*CNS* : *Central Nervous System.*

## 1. INTRODUCTION

Drug Discovery in modern times spans 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 began at the turn of the twentieth century, when new drug structures were discovered, paving the way for a new era of antibiotic development. Rapid improvements in drug discovery happened towards the end of the century, based on these known structures and the introduction of strong new tools such as molecular modeling, combinatorial chemistry, and automated high-throughput screening. Another period was marked by the introduction of recombinant DNA technology, which allowed for the development of potential drug target candidates. Presently drugs can be designed completely from the laboratory based on known structure / activity relationships and drug mechanism analysis. The definition of a drug target is important to link drug response to genetic variance, understand ranked clinical efficacy and safety, explain the differences between drugs in the same therapeutic class and anticipate its practical use in classified patient groups. The success rate of neuropsychiatric drug prospects who enter into clinical trials to effectively reach the market place is 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]. The animal and human analyses needed to ascertain the action of the drug candidate in the body are broad [3] and more difficult to analyse for central nervous system targets because of the blood-brain barrier [4].

“Preclinical studies must establish the safety and potential of the drug before clinical testing with toxicology studies in at least two nonhuman species. These are usually used to determine a projected safe dose range and to provide information about compound distribution, organ-specific toxicity, and metabolism” [5]. Such studies will provide information on possible incidence of adverse effects with increasing dosage and provide guidance on compound-specific surveillance that might be needed in early clinical studies. This is to guide further development of the compound.

### 1.1 A Record of Drug Discovery in Neuroscience

The term ‘drug’ defines any substance that acts on an organism to alter its function, and is used for its medicinal or social effects. Drug sources fall into three main classes; natural, modified and wholly artificial. Natural substances especially plants, animals and minerals, were the main contributors to 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 its 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 given credit for

creating a compound called Laudanum, a 10% opium compound containing 1% morphine, by mixing up natural substances in the 16<sup>th</sup> century. Subsequently, in 1803 Fredrich Sertuner obtained the active substance from the poppy plant which he called morphine, after the Greek god of dreams Morpheus. This provoked enthusiasm for the search for active substances from all natural sources.

## 2. DRUG DISCOVERY PROCESS

The major pharmaceutical companies and large research institutions predominately involve in drug discovery due to the huge resources requirement [9]. This they do by assessing therapeutic agents suitable for human use, analysing the potential for harm [10] and elucidating the mechanisms of the drugs [11]. Researchers discover new drugs through a variety of procedures including:

- 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.

Thousands of compounds may be possible candidates for development as a medicinal therapy at this point in the process. However, after preliminary testing, only a few number of chemicals appear to be promising and warrant further investigation. The process of going from the basic science laboratory to the clinic begins once a promising drug has been found. 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 pre clinical experiments are conducted with animals in the laboratory [12] while the clinical trials are conducted in humans [13].

### 2.1 Preclinical 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 pre clinical 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 pre clinical data-based studies are carried out in research laboratories using non-human creatures and adhering to established customs [14,15]. Representative forms of such studies 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 neuroleptis – 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

### 2.1.1 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.

### 2.2 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 [26], the degrees of

variability by size and genetic makeup produces variations in reaction to and interaction with drugs [26]. "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" [27].

### 2.2.1 Clinical trials design

Clinical trials are created by researchers to solve particular research questions about a medical product. These studies adhere to a set of guidelines devised by the researcher. Researchers analyze existing knowledge on the drug to establish research questions and objectives before starting a clinical trial. 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

### 2.2.2 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:** This phase of the study involves the use of very low doses of the drug to monitor 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. About 70% of administered substances 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. Close to 33% of drugs are approved for 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.

## 3. 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

### 3.1 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 regulatory agency 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]. If developers want to make significant changes to the initial NDA, they must file a supplemental application. In general, any changes to the formulation, labeling, or dose strength must first be approved by RA. Sponsors would file an Investigational New Drug (IND) application if they wanted 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 wanted to conduct additional clinical research or a post-market safety study. 3.2 Drug Advertising.

The RA modulates prescription drug public promotion and 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.

### 3.2 Bio-Equivalence Studies

Only the sponsor has the right to market the drug exclusively when they are approved for marketing. On the expiration of the patent, other drug manufacturers can develop generic version of the drug. Generic drugs have the same dosage form, strength, safety, quality, performance characteristics and intended use as brand name drugs. 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).

## 4. MODERN DRUG PROCESSES IN NEUROSCIENCE

Chemical synthesis from rational design of new molecules is the primal source for drug discovery in modern times; other sources include screening for biological activity in large numbers of natural products and chemical modification of a known active molecule. Successful candidates do 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 pharmacokinetic studies using technologies suitable for non-radio labelled drug molecules” [31]. “Nanotechnology has been applied in the design of new drugs that successfully overcomes the constraints imposed by the blood–brain with an understanding of the physicochemical properties of the said drug and how it engages the BBB to avoid undesired side effects. Several of these drug delivery systems have shown excellent potential in drug delivery across the BBB while manifesting small adverse effects” [32,33].

## 5. NAMING OF DRUGS

A substance that becomes officially approved as drug may have at least five different names; a

chemical name (indicating the drug's 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) [34]. Thus acetaminophen, paracetamol and panadol all refer to the same N- amino para phenol.

## 6. CONSTRAINTS OF DRUG DISCOVERY IN NEUROSCIENCE

The challenges drug discovery in neuroscience are attributable to a variety of factors, including the nature 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 [35].

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 blood brain barrier (BBB) and the blood-spinal cord barrier [35]. These barriers of central nervous system (CNS) act as a selectively permeable membrane and do not completely block all of the incoming compounds [36].

“The primary function of the blood brain barrier 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” [35]. The blood brain barrier is made up of a network of endothelial cells, astroglia, pericytes, perivascular macrophages, and a basal lamina. Most organs of the body are perfused by minute blood vessels lined with endothelial cells that have small pores to allow for the rapid movement of small molecules into the organ interstitial fluid from the movement of blood through the heart and blood vessels [36,38]. 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 [39].

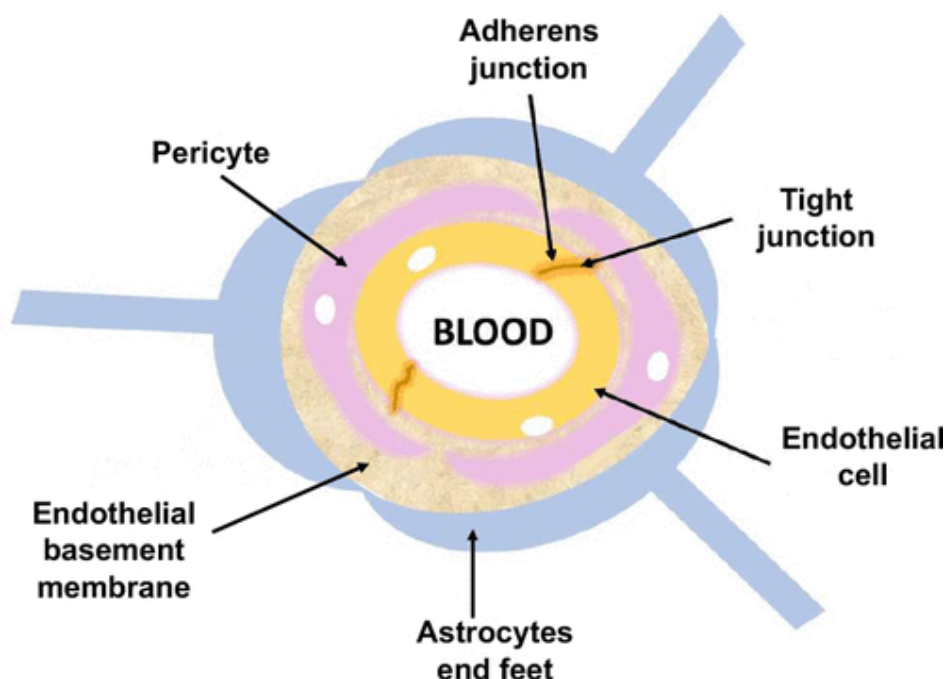
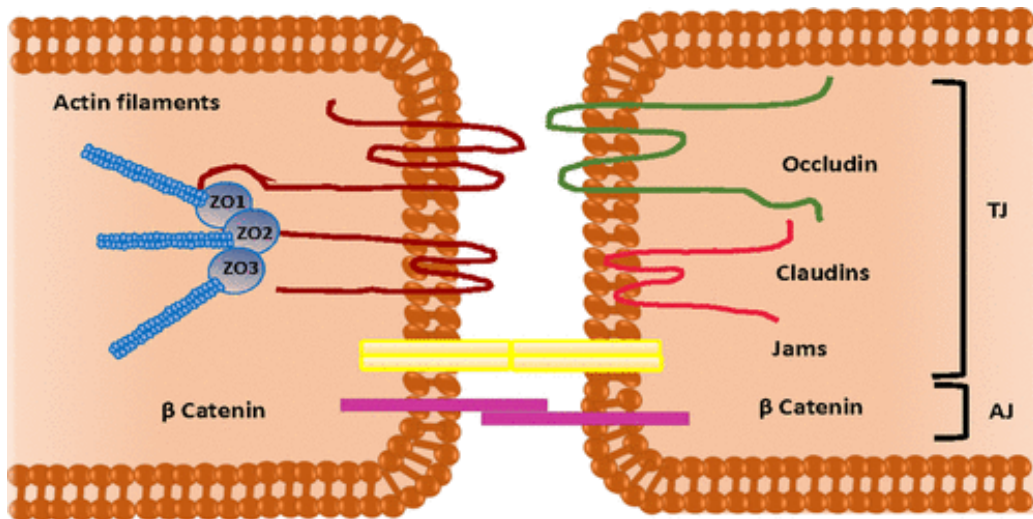


Fig. 1. Schematic drawing of the blood brain barrier [37]



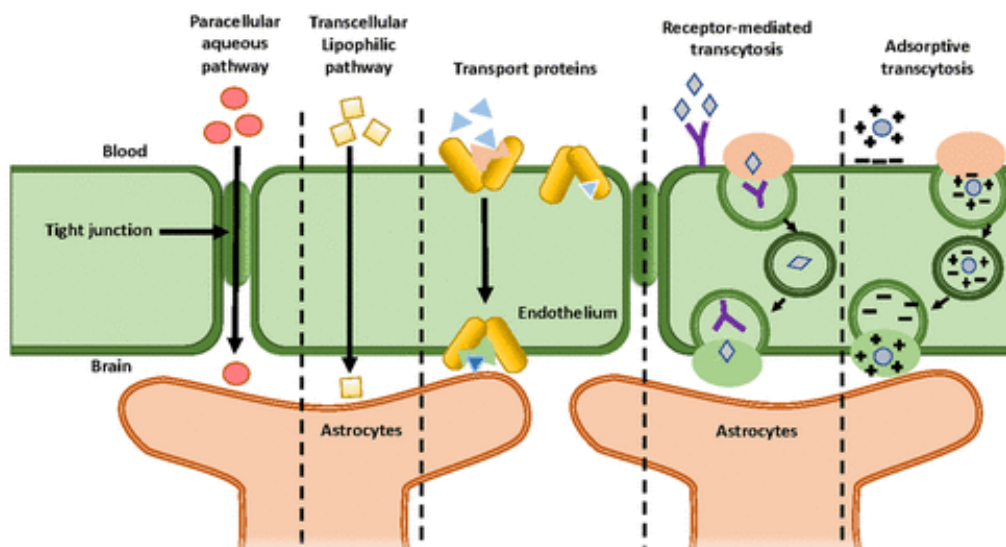


**Fig. 2. A diagrammatic description of tight junctions and adherence junctions between endothelial cells [37]**

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 blood brain barrier 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.

In Parkinson's disease for instance, it was found that there is a brain deficiency of dopamine in

patients with Parkinsonism. Logically it should be possible to give such patients dosages of dopamine and cure their ailment but this is made difficult by the blood-brain barrier as dopamine will not cross it, even if injected directly into the blood stream. But laevo dopa, the chemical precursor of dopamine, can be absorbed across the blood-brain barrier by active transport. Once in the brain, laevo dopa is transformed into dopamine and regulates motor coordination. Laevo dopa has been successfully used in the treatment of Parkinsonism because it is able to cross the blood-brain barrier and reach the intended site of action.



**Fig. 3. Conventional diagram of the different mechanisms for crossing the blood brain barrier [37]**



Another challenge of drug discovery in neuroscience is the presentation of side effects typical with anti psychotic drugs. Most of these drugs 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 [40,41]. 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 [42]. 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 [43].

Many animal models are predicated on a better understanding of human genetics, but these genetic models come with their own variety of challenges. Observations that individual genes and variations may have relatively little impacts and may not be fully penetrate are among these challenges. Furthermore, large-effect variations frequently generate clusters of symptoms, making interpretation even more difficult; strong-effect risk factors may not be shared across species. The animal's genetic background can make phenotyping more difficult to interpret. Existing animal models for various nervous system illnesses do not replicate the disease's major pathologic traits or symptoms, making it difficult to establish whether a treatment would be successful. There will never be a single model for highly varied disorders like schizophrenia, but rather numerous models for different characteristics or subtypes of the condition. The fact that certain features of the human nervous system are not reproduced in nearly any other animal complicates disease modelling even further.

“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” [44]. The challenge of paucity of novel neuropsychiatric drugs can be bridged by addressing them with the following recommendations for potential solutions. First and foremost, we must focus our efforts on human data. Second, we need to think more carefully about animal models, embracing them as tools to test pathophysiological alterations. Third, we must devise ways for selecting more homogeneous patient groups in clinical trials. Fourth, translational biomarkers that may be used for pharmacodynamic assessments as well as patient selection must be developed and validated. Finally more funding should be channelled towards improved infrastructure and workforce training for neuroscience research.

## 7. CONCLUSION

Serendipity used to be the source for drug discovery but rational design is currently the main stay. It takes a longer than average time for the drug discovery process in neuroscience. The main challenge being the ability of drugs to perfuse the blood brain barrier followed by poor infrastructure and trained personnel. This can be intensified with improved funding for infrastructure and workforce training.

## DISCLAIMER

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 we do not intend to use this review as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by any producing company rather it was funded by personal efforts of the authors.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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