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A Perspective Study: Preclinical Screening of Anti-Depressant Activity.

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ABSTRACT:
Much of the current understanding about the pathogenesis of altered mood, impaired concentration and neurovegetative symptoms in major depression has come from animal models. However, because of the unique and complex features of human depression, the generation of valid and insightful depression models has been less straightforward than modeling other disabling diseases like cancer or autoimmune conditions. Today's popular depression models creatively merge ethologically valid behavioral assays with the latest technological advances in molecular biology and automated video-tracking. This chapter reviews depression assays involving acute stress (e.g., forced swim test), models consisting of prolonged physical or social stress (e.g., social defeat), models of secondary depression, genetic models, and experiments designed to elucidate the mechanisms of antidepressant action. These paradigms are critically evaluated in relation to their ease, validity and replicability, the molecular insights that they have provided, and their capacity to offer the next generation of therapeutics for depression.

Keywords: Animal models, Antidepressants, Behavioral testing, Depression Resilience, Stress, Vulnerability

I. INTRODUCTION:

PRECLINICAL STUDY

Preclinical studies refer to **the testing of a drug, procedure or other medical treatment in animals before trials may be carried out in humans.** During preclinical drug development, the drug's toxic and pharmacological effects need to be evaluated through in vitro and vivo laboratory animal testing.

The FDA requires sponsoring companies to develop a pharmacological profile, determine toxicity in at least two species of animals and conduct short-term toxicity studies. Various preclinical requirements exist for different kinds of laboratory animals. Information gathered in preclinical studies are used as evidence and support in FDA applications for the approval of new drugs and medical procedure.

OBJECTIVES OF PRECLINICAL STUDIES:

- The purpose of pre-clinical study is to develop adequate data to decide that it is reasonably safe to proceed with human trials of the drug.
- Means, a laboratory test of a new drug or a new medical device, usually done on animal subjects, to see if the treatment really works and if it is safe to test on humans.
- However the main objective is to collect the data to submit to the FDA for IND filing.

PRECLINICAL DEVELOPMENT:

In drug development, **preclinical development,** also termed **preclinical studies or nonclinical studies,** is a stage of research that begins before clinical trials (testing in humans) and during which important feasibility, iterative testing and drug safety data are collected, typically in laboratory animals.

The main goals of preclinical studies are to determine a starting, safe does for first-in-human study and assess potential toxicity of the product, which typically include new medical devices, prescription drugs, and diagnostics.

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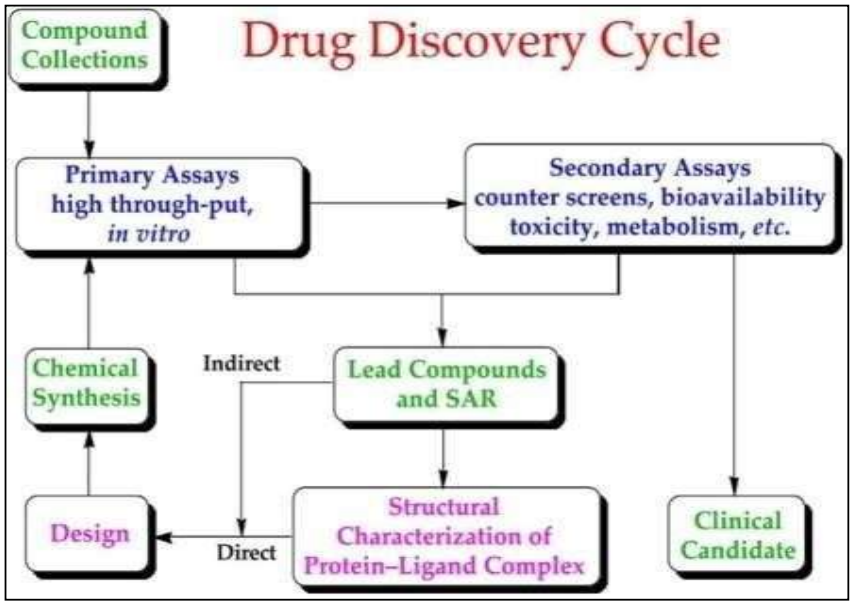

Fig. 1 Drug Discovery Cycle.

TYPES OF STUDIES IN PRECLINICAL TRIALS

Preclinical trials, also known as non-clinical trials are the laboratory tests of a new drug, device or medical treatment on preclinical studies is to see whether the drug or the treatment really works and whether it is safe to test on humans.

Thus, the main goal of a preclinical research is to collect sufficient data and establish the safety profile of the drug or the treatment under question. And to fulfill this objective, various types of studies are carried out in a preclinical trial.

Types of studies and their significance in a preclinical studies:

1. Screening test:

It's a simple and rapidly performed initial screening test to determine the presence or absence of a particular pharmacodynamic activity in the new drug. E.g.determination of analgesic or pain relieving activity in the new drug.

2. Test on isolated organs and bacterial cultures:

These are few preliminary tests to determine specific activity in the new drug like anti- histaminic, anti-bacterial, anti-secretory, vasodilation etc. Healthy organs isolated from dead animals or bacterial cultures are used for these

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preliminary tests.

3. Tests on animal models:

Animal models like rat, pig, mouse, hamster, and rabbit are used to determine the actual effects of the drug in a live organism. After successful results in initial stages, higher animals like cats, dogs, and monkeys are used for preclinical trials.

4. General observational test:

The drug under the trial is injected in tripling doses to a small group of mice which are then observed for any hidden effects.

5. Confirmatory tests and analogous activities:

Compounds which yield a desirable result are carried forward in the trial for more complex tests. Other activities like antipyretic and anti-inflammatory are further determined for an elaborate examination of the drug properties.

6. Mechanism of action:

Experiments are conducted to determine the mechanism of the action of the drug. Eg. if the drug is an anti-hypertensive drug, whether it is an alpha or beta blocker, ACE inhibitor or calcium channel blocker.

7. Systemic pharmacology:

Besides determination of the action of the drugs, its effects on individual and major organ systems like nervous, cardiovascular, respiratory, and renal are also examined. This can givea clue about any possible side-effects of the drug on any major organ system.

8. Quantitative test:

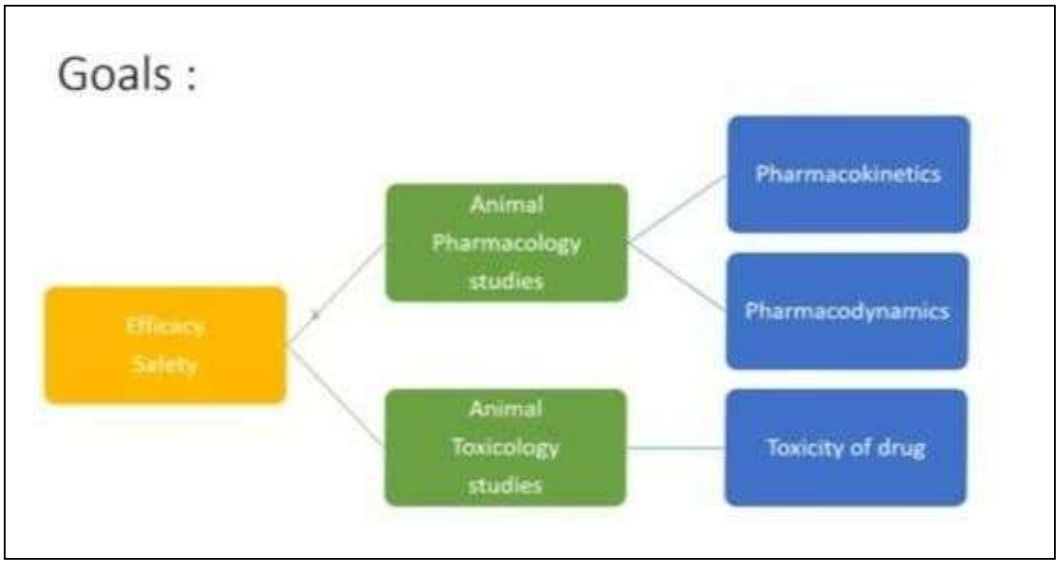
It includes examination of the dose response relationship, maximal effects, and comparative efficacy of the new drug with the existing drug, thus establishing the market value of the drug.

9. Pharmacokinetics:

It involves the study of the movement of the drug substance in the body of the living organism which includes the processes of absorption, distribution, metabolism, localization in tissues and excretion from the body. They help to know the safe dose and preferred route of administration for the drug.

10. Toxicity test:

Both short-term or acute and long-term or chronic toxicity testing are carried out to determine the toxic effects of the drug and mortality in animal models.



ANIMALS USED IN TESTING OF ANTI DEPRESSANTS

1. Male Sprague Dawley rats
2. Albino-Swiss rats.
3. Male Wistar rats.
4. Macca fasicularis or female cynomolgus monkeys for post partum depression.

ANIMAL TESTING

The information collected from these studies is

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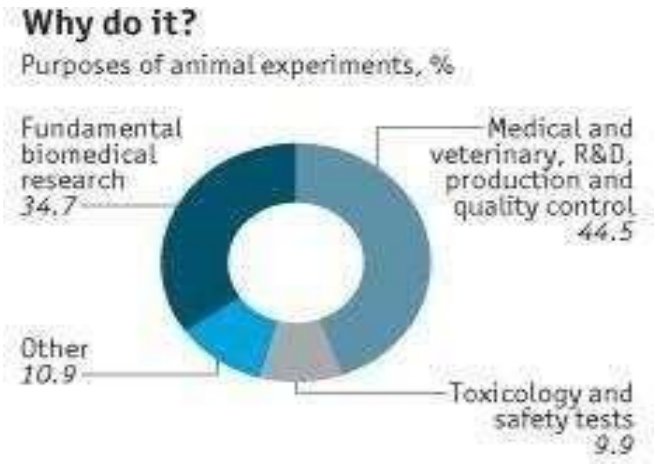
vital so that safe human testing can begin. Typically, in drug development studies animal testing involves two species. The most commonly used modelare murine and canine, although primate and porcine are also used.

- **Choice of species**

The choice of species is based on which will give the best correlation to human trials. Differences in the gut, enzyme activity, circulatory system, or other considerations make certain models more appropriate based on the dosage form, site of activity, or noxious metabolites. For example, canines may not be good models for solid oral dosage forms because the characteristic carnivore intestine is underdeveloped compared to the omnivore's, and gastric emptying rates are increased. Also, rodents cannot act as models for antibiotic drugs because the resulting alteration to their intestinal flora causes significant adverse effects. Depending on a drug's functional groups, it may be metabolized in similar or different ways between species, which will affect both efficacy and toxicology. Medical device studies also use this basic premise. Most studies are performed in larger species such as dogs, pigs and sheep which allow for testing in a similar sized model as that of a human. In addition, some species are used for similarity in specific organs or organ system physiology (swine for dermatological and coronary stent studies; goats for mammary implant studies; dogs for gastric and cancer studies; etc.).

Importantly, the regulatory guidelines of FDA, EMA, and other similar international and regional authorities usually require safety testing in at least two mammalian species, including one non-rodent species, prior to human trials authorization.

Fig. 2 Purpose of Animal Testing.



ETHICAL ISSUES

Animal testing in the research-based pharmaceutical industry has been reduced in recentyears both for ethical and cost reasons. However, most research will still involve animal based testing for the need of similarity in anatomy and physiology that is required for diverse product development.

1. The Ethics of Animal Models in Preclinical Testing

Preclinical testing is vital for assessing the safety profiles and efficacy of new therapeutics in development. Animal testing is one of two routes usually selected for the preclinical stage, the other being testing on human cell cultures in vitro.While scientists must provide a sound rationale for choosing the animal model over the in vitro methodology to ensure that animal models are used only when absolutely necessary, the topic of the ethics of using animal models at all in preclinical testing remains hotly debated. Here, we will discuss this theme in depth, and conclude on the current stance taken by the scientific community.

2. Ethical Considerations of Preclinical Testing

It has been estimated that of every 5000 new drug development projects that make it through initial computer modelling and in-vitro testing, only 5 will ever successfully pass preclinical tests which are mandatory before clinical testing in humans. Moreover, of those

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drug developments that successfully pass the preclinical testing phase, only 5 % ever make it to the market as a licensed treatment for humans. Essentially, that suggests that there is less than a 0.1 % chance of a successful drug product being developed from inception to market. Although these statistics justify why drug companies must charge accordingly to recover their cost outputs which includes all the costs of the majority of failed projects, it cannot ethically justify the number of animals that are sacrificed in order to achieve this high failure rate.

There is this vast chasm between preclinical testing in animals and the eventual successful outcome of clinical trials in humans into which the majority of these drug trials disappear. In order to compensate or reduce this failure rate, additional safeguards must be placed on which drugs do make it to the animal testing phase to at least ensure that the percentage of drugs successfully passing preclinical trials is much higher than the current 0.1 %. We cannot do much at our current level of testing and knowledge to increase the translational level of success between animals and humans, since that is still not fully understood why a drug is successful in one species and not another, but we certainly can narrow the gap between drugs that appear to have great potential in the computer modelling and in- vitro stage, only to fail when they are introduced into animals.

PRECLINICAL SCREENING OF ANTI-DEPRESSANTS:

Depression:

- Depression is the most common of the affective disorder(defined as disorders of mood rather than disturbance of thought or cognition); it may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions.
- Depression is not a homogeneous disorder, but a complex phenomenon, which has many subtypes and probably more than one etiology.
- Depression symptoms can vary from mild to severe and can include:-

i. Feeling sad or having a depressed mood
ii. Loss of interest or pleasure in activities once enjoyed
iii. Changes in appetite – weight loss or gain unrelated to dieting
iv. Trouble sleeping or sleeping too much
v. Loss of energy or increased fatigue
vi. Increase in purposeless physical activity(e.g.hand wringing or pacing) or slowed movements and speech (actions observable by others).
vii. Feeling worthless or guilty
viii. Difficulty thinking, concentrating or making decisions,Thoughts of death or suicide.

Risk Factors for Depression:

- Depression can affect anyone-even a person who appears to live in relatively ideal circumstances.
- Several factors can play a role in depression:

1. Biochemistry: Differences in certain chemicals in the brain may contribute to symptoms of depression.
2. Genetics: Depression can run in families. For example, if one identical twin has depression, the other has a 70 percent chance of having the illness sometime in life.
3. Personality: People with low self-esteem, who are easily overwhelmed by stress, or who are generally pessimistic appear to be more likely to experience depression.
4. Environmental factors: Continuous exposure to violence, abuse or poverty may make some people more vulnerable to depression.

TYPES of Antidepressant Drug:-

Antidepressant drugs fall into the following categories:

1) Inhibitors of monoamine uptake.
2) Monoamine receptor antagonists.
3) Monoamine oxidase inhibitors (MAOIs).

1) Inhibitors of Monoamine uptake:

- Selective serotonin (5-HT) reuptake inhibitors(SSRls) (e.g.**fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram**).
- Classical tricyclic antidepressants (TCAs) (e.g. **imipramine, desipramine, nortriptyline, amitriptyline, clomipramine).** These vary in their ability to inhibit noradrenaline and 5-HT reuptake.
- Newer, mixed 5-HT and noradrenaline reuptake inhibitors (e.g. **venlafaxine**{somewhat selective for 5-HT},**desvenlafaxine, duloxetine, milnacipran**).
- Noradrenaline reuptake inhibitors (e.g. **bupropion, reboxetine, atomoxetine**).

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2) Monoamine receptor antagonist:

- Drugs such as **mirtazapine, trazodone, mianserin** are non-selective and inhibit a range of amine receptors including presynaptic a2 adrenoceptors (autoreceptors) and 5-HT2 receptors. They may also have weak effects on monoamine uptake.

3) Monoamine oxidase inhibitors (MAOIs):

- Irreversible, non-competitive inhibitors (e.g. **phenelzine, tranylcypromine)**, which are non-selective with respect to the MAO-A and MOA-B subtypes.
- Reversible, MOA-A selective inhibitors (e.g. moclobemide).

DRUG SCREENING METHODS

- **In vitro methods-**

1) Inhibition of (3H)-norepinephrine uptake in rat brain synaptosomes.
2) Inhibition of (3H)-dopamine uptake in rat striatal synaptosomes.
3) Inhibition of (3H)-serotonin uptake in synaptosomes.
4) Binding to monoamine transporters.
5) Radio ligand binding assay.

- **In vivo methods-**

1) Catalepsy antagonism in chicken.
2) Despair swim test.
3) Tail suspension test in mice.
4) Muricide behaviour in rats.
5) Potentiation of nor epinephrine toxicity.

DURATION OF STUDY

- **In-vitro Studies:**

Usually 1-3 hours is utilized for the in-vitro preclinical studies. The time may extend because of the preparation of the tissue or depends on the type of bioassay employed for the study.

- **In-vivo Studies:**

The duration of study may vary from 24 hours to about 15 days as per the method employed.

1. Catalepsy antagonism in chicken – 5 days
2. Despair swim test –24 hrs
3. Tail suspension test – 5-6 min.
4. Learned helplessness in rats - 5 min. maximum

II. CONCLUSION

From the above studies we conclude that depression is a serious mood disorder and its need to be treated carefully and properly. Depression occurs due to deficiency in the biogenic monoamine such as serotonin (5HT), dopamine (DA) and noradrenaline (NA). The treatment with antidepressants are done on the basis of their ability improve monoaminergic transmission. Behaviour, thoughts, genetics, and environment plays vital role in depression. Psychotherapy is very useful in treating depressed patients. We understand about different causes of depression and the different types of depression. The type of medication which we have to take in different type of depression. The screening models help us to find out the efficacy of a novel drug with respect to a standard drug. We can also find out efficacy of a pre-existing drug with help of screening models. We cannotignore depression, the depression person must treated properly.

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