ISSN – 2277-7911
Impact Factor – 5.077

YOUNG RESEARCHER
A Multidisciplinary Peer-Reviewed Refereed Research Journal

Oct-Nov -Dec 2023
Vol. 12 No. 4

ADVANCEMENTS IN ANTIDEPRESSANT MEDICATIONS THROUGH DESIGN, DEVELOPMENT, AND STANDARDIZATION

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DOI - 10.5281/zenodo.10839987

ABSTRACT:

An emphasis on the complex elements of their conception, creation, and standardisation, this abstract examines the most current developments in the field of depressive drugs. Understanding the intricate neuroscience of depression has advanced significantly over time, resulting in the discovery of new molecular targets. Drugs that target particular neurotransmitter systems, such as dopamine, norepinephrine, and serotonin, are developed during the design phase with a focus on reducing adverse effects and enhancing overall efficacy. To improve bioavailability and patient compliance, novel formulations, delivery methods, and routes for drug delivery are incorporated into the development process concurrently. Additionally, standardisation initiatives seek to create uniform testing and assessment procedures for antidepressant drugs, promoting a more thorough and trustworthy appraisal of their therapeutic potential. The thorough investigation of these interrelated facets shows how antidepressant drugs have been evolving continuously, offering hope for the advancement of mental health care.

Keywords: Antidepressant, Advancement, Medications, Design, Development, Standardization.

INTRODUCTION:

Antidepressants are a class of drugs that are primarily used to treat depressive disorders and anxiety disorders. However, this group of drugs is also used to treat some behavioural disorders, enuresis, desire control issues, nutritional disorders, and sexual brokenness. Over time, a multitude of antidepressant classes have emerged in India; some have endured and are currently in use, while others are no longer recommended or ranked as #1 by physicians. The investigation into the efficacy of antidepressants in India has mostly followed western trends; nevertheless, some of the more prominent drugs have not received the same level of evaluation as others. The majority of studies conducted in India have evaluated several antidepressants in suffering. Few studies have evaluated antidepressants for illnesses other than debilitating disorders. This page focuses on various antidepressant studies conducted in India. The review will

focus on the analysis published in the Indian Journal of Psychiatry and the research described in PubMed ordered diaries regarding the viability, sufficiency, usefulness, and morality of antidepressant use in human beings.

Efficacy/effectiveness in Depression:

The preliminary research on the viability of antidepressants can be divided into four categories: studies evaluating an upper (no comparator studies), studies evaluating the suitability of a stimulant with fictitious treatment as a comparator, studies examining the suitability of two dynamic medications, and studies evaluating the viability of antidepressants with various treatment modalities such as mental treatment or electroconvulsive therapy.

LITERATURE REVIEW:

Myin-Germeys et al. (2018) offer a thorough synopsis of the scientific and practical developments in ESM, highlighting its potential to improve our comprehension of mental health issues. The authors stress the value of ESM in capturing fleeting changes in mood, thought processes, and social interactions. They also stress the method's ecological validity and capacity to get over the retrospective biases inherent in more conventional assessment techniques. The study addresses the integration of ESM with technical improvements as a crucial factor. By enabling participants to record their experiences in real-time and in their native contexts, cellphones and other mobile devices enable more ecologically valid data collecting. By reducing recollection biases and improving data precision, this integration offers a more accurate depiction of people's mental states. The writers also address compliance and data protection issues, stressing the importance of taking ethics into account when putting ESM into practice. The study colleagues provides a thorough overview of the developments in ESM and provides insightful information on its technological advancements and ability to completely transform the field of mental health research. The significance of ESM as a flexible and sophisticated methodology in the field is highlighted by the integration of technology, ethical considerations, and an emphasis on temporal dynamics.

Peng et al. (2013), A thorough analysis of the most recent advancements in the medicinal chemistry of coumarin compounds is provided who also provide insight into the structural variety, biological activity, and new directions in drug discovery of these molecules. The review commences with a synopsis of the structural attributes of coumarins, highlighting the function of their central scaffold in regulating pharmacological actions. The authors explore the several synthetic approaches used to alter the structure of

coumarins, emphasising the effects of these changes on pharmacokinetics and bioactivity. For medicinal chemists looking to create novel coumarin derivatives with improved therapeutic characteristics, this area is an invaluable resource.

Dimidjian et al. (2006) carried out a ground-breaking randomised experiment. The study evaluated these three commonly used therapeutic techniques with the goal of providing evidence-based treatment recommendations for major depression, a common and debilitating mental health illness.The study's findings have significant ramifications for the management of major depression since they imply that, during the acute stage of the condition, behavioural activation and cognitive therapy may be just as beneficial as antidepressant drugs. This has aided in the increasing understanding of the benefits of psychotherapy interventions as stand-alone or adjunctive therapies for depression. The significance of customising treatment plans to each patient's preferences and unique traits was further emphasised by the study.

Congreve et al. (2008). Using short, low molecular weight fragments as the basis for drug design, fragment-based drug discovery has become well-known as an inventive method for finding lead compounds in the early phases of drug development. Overall, the study highlights the importance of FBDD in contemporary drug development and advances our knowledge of its foundations and uses. Finding novel chemical space and prioritising efficiency make FBDD a compelling and effective method for producing high-caliber drug candidates.

Becker and Greig (2010), who emphasised the gap in knowledge that exists between preclinical research and clinical results. The review concentrated on the challenges researchers faced in converting promising preclinical results into neuropsychiatric diseases treatments that work. In order to close the translational gap, the assessment emphasises the necessity of better coordination between fundamental scientists, physicians, and industrial players. Moreover, it promotes a deeper comprehension of the neurology of mental illnesses and the creation of novel tactics, including personalised medicine methods, to increase the effectiveness of neuropsychiatric medication development.

THE DEVELOPMENT HISTORY OF ANTIDEPRESSANT DRUGS:

Since the time of the ancient Greeks, compound experts have been recognised to have stimulating effects, and Poppy was even approved as a means of easing "distress." Of course, the presence of opium was the reason for this apparent impact. Even in the 1800s,

"opium fixes" were employed to treat depression. Elective specialists such as hematoporphyrin, reserpine, and dinitrile succinate have also begun to be involved historically as of late. Furthermore, there is evidence that in the 1930s, amphetamines were used to alleviate melancholy in patients. In any event, important developments in the development of stimulant medications today did not begin until after the middle of the 20th century.

Anticholinergic specialists who were known to have mental effects were typically used to treat patients with depression in the mid-1950s (e.g., chlorpromazine, thioridazine, levomepromazine). Nevertheless, the discovery of two specific experts—the tricyclic stimulant (TCA) imipramine and the monoamine oxidase inhibitor (MAOI) iproniazid—led to a significant advancement in medication development. These experts brought with them an improved understanding of the role those endogenous substances, such as serotonin, norepinephrine, and dopamine, play in altering one's mindset. Due to the development of other TCA specialties (such as amitriptyline and desipramine) that had fewer side effects than its progenitor, the usage of TCAs expanded during the 1960s. At the same time, the disclosure of a few negative effects, dietary restrictions, and drug collaborations made MAOI experts unpopular.

As mental evaluation continued throughout the 1970s, talk and debate centred on the importance of serotonin and norepinephrine (either concurrently or exclusively) for the successful treatment of people suffering from depression. Still, during the 1980s, pharmacological development began to focus on serotonin as a key target for the treatment of stimulants. The approval (1985) and quick withdrawal (1986) of bupropion, a norepinephrine/dopamine take-up inhibitor, due to seizures, may have contributed to this shift. Shortly after, in 1987, fluoxetine became the first selective serotonin reuptake inhibitor (SSRI) approved by the US Food and Drug Administration (FDA).

As of right now, important consideration doctors were increasingly endorsing stimulant medications. This change has been attributed to SSRIs' superior decency when compared to other recently developed medications. During this time, stimulant specialists also began to be used for symptoms other than discouragement, such as discomfort. Additionally, there has been considerable development in the prescriptions for optional drugs like venlafaxine, which affect serotonin and norepinephrine.1. These events most likely contributed to the increasing prevalence of energizer use in the

United States, which increased by around 400% between 1988 and 2008.

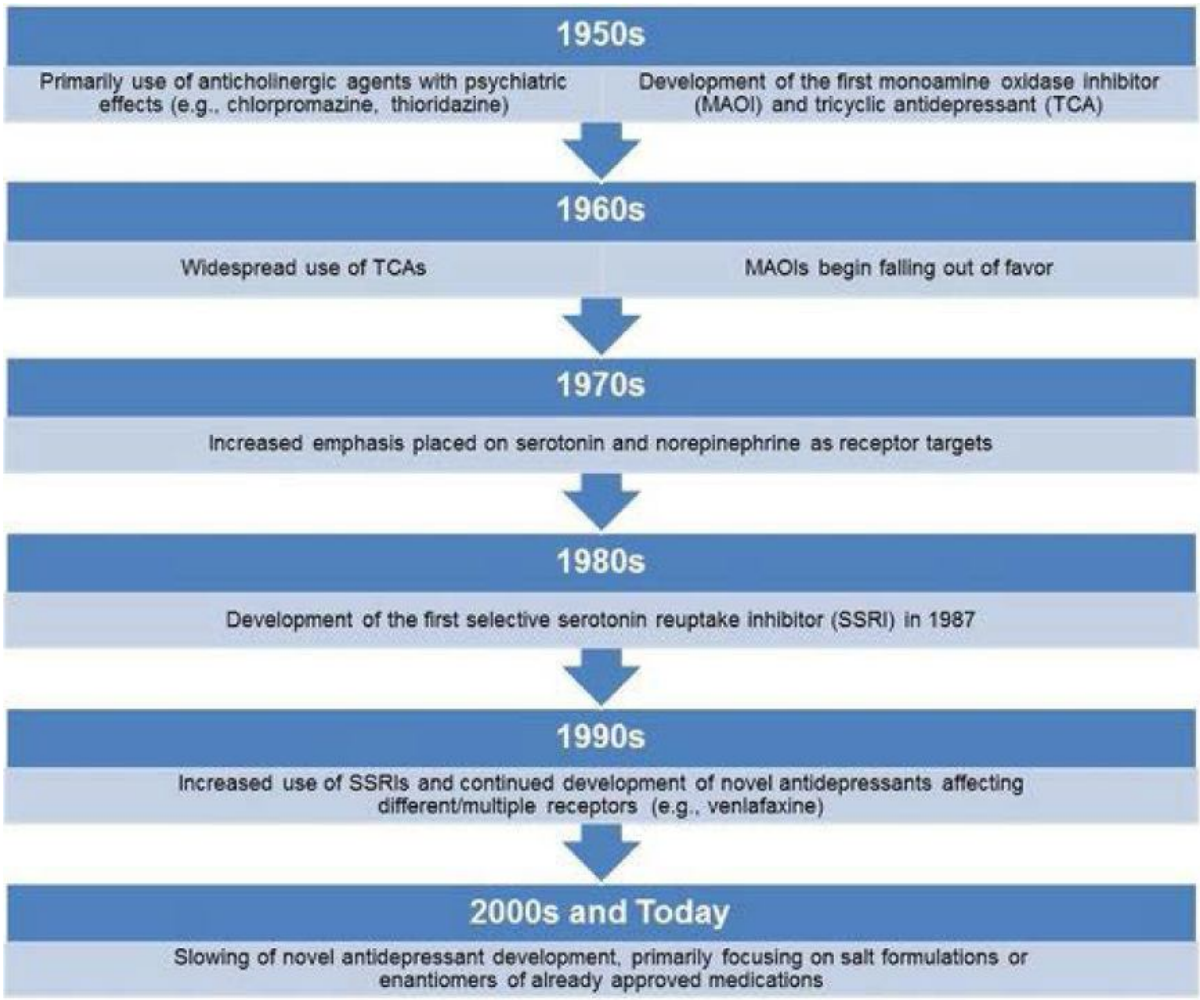

Figure 1: Significant Advances in Antidepressant Treatment

The approval of innovative antidepressant pharmaceuticals appears to have slowed down recently, as some of the recently approved drugs (such as desvenlafaxine, escitalopram, and bupropion hydrobromide) are chemical enantiomers or different salt formulations of previously approved drugs. Furthermore, it has been proposed that these drugs' tolerability has increased but their efficacy has not since the 1950s. The FDA's antiquated antidepressant approval rules, which do not encourage firms to attain higher levels of symptom relief or target novel disease pathways, may be contributing to this stoppage of novel drug research. This article will provide as an overview of the FDA's approval procedure, go over the criteria the agency looks at when assessing antidepressant drugs, and talk

about the need for revised rules defining antidepressant efficacy.

SUMMARY OF THE PROCEDURE FOR DRUG APPROVAL:

The FDA is responsible for ensuring the safety and suitability of drugs, antibodies, biologics, nutritional supplements, medical devices, food supplies, and cosmetics. The Centre for Medication Assessment and Exploration (CDER), one of the largest divisions within the FDA tasked with overseeing clinical items, is in charge of evaluating and approving doctor-prescribed medications in humans.

An overview of the drug endorsement procedure is provided in Figure 2, which typically starts with the creation of a new atomic element (NME). These products either comprise a functioning moiety that is closely linked to a previously supported product (such as an alternative salt or ester) or a completely new dynamic moiety that has not yet received FDA approval (sometimes referred to as "another synthetic element"). The pharmacologic action of the NME should then be tested in various research centres and creature models by a pharmaceutical designer. The designer should submit an Investigational New Medication (IND) application to CDER once they are ready to test the atom in humans. Preclinical data on creature pharmacology and toxicity research, fabrication considerations (e.g., strength, creation tactics), and detailed guidelines for the suggested clinical examinations in human subjects are all included in this application.

Figure 2: The Procedure for Drug Approval

To demonstrate the safety and efficacy of a novel product, drug inventors must file an IND application and then complete satisfactory, strictly controlled clinical preliminary work. In general, these tests ought to be approved by an institutional survey board; they ought to have a standard that describes the goals, determination models, test size, and inquiry strategies; they ought to use a review plan that allows for a valid correlation with a control (such as a dynamic control, fictitious treatment control, portion examination control, or verifiable control); they ought to use techniques to guarantee the validity of the data obtained (such as measures to limit predisposition); and they ought to

provide an analysis of the results that is sufficient for evaluating the effects of the medication.

These clinical assessments are often carried out in stages. The primary goal of stage I studies, which are mostly carried out on healthy subjects, is to ascertain the pharmacokinetic effect of the drug on people as well as the extent of harm and the range of acceptable measurements. Stage II examinations are small-scale, controlled preliminary exams used to assess a certain number of patients' viability and relative wellbeing. Lastly, stage III preliminary studies are more meticulously observed research endeavours intended to obtain additional data on the sufficiency of specific indicators and more accurate health information. In general, the FDA looks for "significant proof" of adequacy to warrant endorsement, which is demonstrated by about two adequate and highly monitored examinations. It's critical to keep in mind that, by this measure, the quantity of "negative" research does not always imply endorsement.

Once the drug designer has overseen these early processes and gathered sufficient evidence to demonstrate the safety and efficacy of the examined substance, they should submit Another Medication Application (NDA) to CDER. Through the NDA process, the pharmaceutical engineer "officially recommends that the FDA support another drug available to be purchased and advertised in the US". Expanding upon the information in the IND, the NDA's contents allow CDER to confirm the medication's safety and appropriateness for the proposed sign, assess the suitability of the recommended marking (like bundle embed), and ascertain whether the recommended fabrication techniques are sufficient to guarantee the item's strength, quality, and flawless condition.

CLINICAL CHALLENGES:

Clinicians should base their gloom therapy strategies and symptomatic categorization on the extremely complex clinical phenomenology of melancholy, as there is no clear natural cause for the disorder. The tenth Modification of the Worldwide Factual Characterization of Illnesses and Related Medical Conditions and the fifth edition of the Demonstrative and Factual Manual of Mental Problems both include symptomatic measures for burdensome issues that require the singular to exhibit roughly five out of nine side effects virtually every day for at least fourteen days. These five side effects should include either a burdensome state of mind or an indifference or joy. The Hamilton Rating Scale for Wretchedness and the Montgomery-sberg Misery Rating Scale are commonly used to evaluate the severity of

troublesome issues. This leads to the unfounded suspicion that everything on the scale (and, thus, all nine of the side effects surveyed to analyse discouragement) are of equal analytical weight. Both of these widely used scales use the total score of everything on the scale as their proportion of the seriousness of sorrow. There are, after all, many different clinical subtypes of suffering. For example, three of the nine analytic side effects—such as sleep deprivation or hypersomnia, psychomotor hindrance or psychomotor fomentation, and weight reduction or weight gain—are considered present if they are more than or not exactly typical, and other side effects exhibit variable signs.

Taking into account this suggestive adaptability, individuals who fit the models for a "burdensome issue" can experience 1497 different combinations of adverse symptoms. It is theoretically possible for each of these groups of unrestricted side effects to have unique genetic, natural, and, most importantly for the current discussion, pharmacological reactions. As a result, comparing scores on the HAM-D, MADRS, or another measure of suffering across different individuals does not demonstrate similarity to the clinical profile of the individuals, and variations in these scales' scores with treatment (which are frequently utilised to determine the appropriateness of medications) likely reflect distinct suggestive changes in different patients. This heterogeneity makes it difficult to repeat findings, which seriously undermines the interpretation of studies aimed at improving new antidepressants as well as those that try to link clinical changes to the neurotic systems of suffering that lie beneath the surface. Naturally, systemic obstacles like as examination, control condition selection, evaluation season, and outcome measure assessment also often limit our ability to learn about the effectiveness of antidepressant treatments.

It is not surprising at all that the treatment's adverse effects are not entirely satisfactory given the lack of accuracy in their designation. There are serious problems with currently available antidepressants, such as high rates of relapse, poor rates of full abatements, substantial side effects that persist after therapy, and delayed delays for side effect goals. According to the Sequenced Treatment Choices to Ease Doom (STAR*D) preliminary, only 33% of patients recovered after a 14-week course of treatment with citalopram at a viable measurement among those who had not recovered, a second course of treatment with an alternative type of stimulant at an adequate dose for an adequate length simply occurred, (best case scenario, in a 30% recuperation rate). One late theory, in light of these

regrettable overall outcomes, is that multi-target sedates, which combine the two antidepressants with non-monoamine-based specialists, may be expected to improve the rates of suffering reduction. Based on this approach, the US Food and Drug Administration (USFDA) approved the introduction of three novel mix specialists in the last three years: vortioxetine, lev milnacipran, and vilazodone. These new drugs offer new options for treating depression, and one of them, vortioxetine, may also be effective in reducing the mental apathy that often accompanies discouragement. The most exciting research on ebb and flow involves ketamine, which has been shown to provide relief from heavy side effects quickly (in about two hours); when inhaled as a shower in the intranasal cavity three times a week for approximately fourteen days, the beneficial effects can last for more than a month. These new methodologies provide new expectations but do not address the fundamental problem of comprehending the relationships between the symptomatology, hidden organic systems, and component of the energizer's activity. These new methodologies require a much wider assessment before they can be recommended for all discouraged people.

DIFFICULTIES FOR RESEARCHERS IN NEUROSCIENCE:

Global approaches for the creative work of novel drugs concentrate on clear-cut clinical situations and make use of standardised methods to assess the feasibility and health of a large number of experts before recommending a specific medication or medications for regular clinical consideration. Nevertheless, innovative work for mental prescriptions is currently primarily based on coordinating (a) clinical examinations that take into account the neurotic changes in the mind and sensory system that occur when explicit clinical conditions are available and (b) fundamental science concentrates on that take into account the clinical side effects that are related with explicit obsessive changes in the cerebrum and sensory system. This is due to the complex clinical introductions and course of illness, obscure pathogenesis, and lack of proper creature models for most mental circumstances. It is challenging to identify physiological markers that can be used to assess the efficacy of interventions aimed at combating and treating depression because there isn't a clear understanding of the neurotic alterations that trigger the onset of melancholy and shape its trajectory. Therefore, current clinical recommendations for assessing the

viability of antidepressants—which apparently don't replicate the underlying organic changes related with discouragement—compel research aimed towards developing novel antidepressants. Flow research can be categorised into four main groups: (a) studies on the prodromal side effects of depression; (b) studies on the pathophysiological alterations that occur with melancholy; (c) studies on the patterns in natural cycles that are triggered by the administration of stimulant prescriptions; and (d) studies on interventions aimed at reducing the relapse into misery.

Recent rapid advancements in neuroscientific methods have given rise to some new theories regarding the pathophysiology of depression. These theories include variations in the function of mind's neurons, abnormalities in brain flexibility, and abnormalities in the hypothalamic-pituitary-adrenal axis. Nevertheless, the evidence for these conjectures is now insufficient to justify using these models as guidelines for the development of novel energizer experts. Chinese neuroscientists are active participants in this global effort, but the promising combinations they have identified in basic research have largely failed when applied therapeutically due to the lack of reliable information regarding the aetiology of discouragement.

THE PHARMACEUTICAL INDUSTRY'S CHALLENGE:

The cost of developing new drugs has skyrocketed in recent years, and it now takes almost twice as long to list new prescriptions for public sale. The evaluated inventive work cost for fluoxetine was approximately 230 million dollars ($US), whereas the assessed cost for duloxetine was approximately 900 million dollars. By 2010, the typical cost of promoting a different drug was several billion dollars. Since there is no way for the pharmaceutical industry to share losses when a bright professional fails to get it to market, large global pharmaceutical companies have understandably grown more conservative as the costs associated with drug development have increased. These moderate systems include shrinking their own testing departments; acquiring licences for synthetic mixtures from universities, research centres, or small-scale drug research centres; and introducing minor modifications to currently approved prescriptions (e.g., altering dosage, administration method, or demonstrated conditions; slightly altering compound design; or combining two medications into a single pill) and promoting them as novel drugs. These profit-driven adjustments actually restrict the research, development, and presentation of new antidepressants.

Despite the rapidly declining investment of global pharmaceutical companies in the development of antidepressants, the anticipated enormous market size for antidepressants could augment the somewhat unpalatable viability of momentum antidepressants and prompt a swift reallocation of research resources towards antidepressants in the event that a truly 'advancement' drug was feasible. Considering its remarkably quick action and seeming suitability in treating treatment-safe depression and hopelessness in bipolar disorder. One such drug is ketamine. There is a plethora of research being conducted on ketamine, which should improve our understanding of the pathophysiology of depression and enable the development of new, effective antidepressant medications.

THE NEED TO COMBINE FORCES:

Global studies on the burden of disease have consistently demonstrated that economic downturns are the primary cause of neuropsychiatric disorders and the primary cause of years spent living with a disability in both high-income countries and low- and middle-income countries. Since destitution has a real impact on the economic development of every country on the earth, the World Bank, the United Nations, and the World Wellbeing Association have recently recognised destitution as a high-need medical condition. Addressing the avoidance, recognition, and effective management of depression is a vital component of global efforts to improve the standard of living and well-being of the entire population.

Handling a problem this magnitude calls for the concerted effort of physicians, experts, pharmaceutical companies, and substantial financial and administrative support from public states. Affected individuals who are grieving, their families, the general public, and the media should also actively participate in the effort to gather the necessary resources and the prolonged political commitment anticipated to address this perplexing problem. It will not be an easy task, considering the different requirements, paths of events, and responsibilities of these different parties.

SIDE-EFFECTS AND SAFETY IN OVERDOSE:

Many adverse effects of the more popular antidepressants may compromise their consistency and perhaps pose a risk. The TCAs have a wide range of adverse effects, many of which are attributed to their numerous and mostly unsuccessful pharmacological activities (Box 1). Due to their affinity for the serotoninergic system, the majority of SSRIs do not exhibit any additional clinically

meaningful pharmacological effects. But because SSRIs affect the serotoninergic system and some 5-HT receptors, they do have adverse effects (Box 2); for instance, increased 5-HT receptor mobility is likely the cause of nausea and vomiting. This issue also includes meta-analyses evaluating the decency-related efficacy of SSRIs and TCAs as well as the side effects of more experienced and current antidepressants and their interactions.

Box 1. Side-effect profile of TCAs

Anticholinergic
Dry mouth, blurred vision, urinary hesitancy, constipation, memory impairment, aggravation of narrow angle glaucoma

Antihistaminic
Sedation

α_1-adrenoceptor antagonism
Orthostatic hypotension

Cardiovascular effects
Sinus tachycardia, arrhythmias, conduction delays, sudden death

Other
Weight gain, sexual dysfunction, impaired cognitive and psychomotor processes skills, convulsions

Box 2. Side-effect profile of SSRIs

Nausea/vomiting
Abdominal pain
Dry mouth
Constipation/diarrhoea
Headache
Asthenia
Dizziness
Insomnia/somnolence
Sweating
Anorexia
Weight loss
Nervousness/agitation
Tremor
Convulsions
Dystonic reactions (paroxetine)
Sexual dysfunction (reduced libido, anorgasmia)

Figure3: Side-Effects Of Antidepressants

CONCLUSION:

To sum up, the continuous progress in the creation, growth, and standardisation of antidepressant drugs heralds a revolutionary period in the field of mental health care. The development of targeted medications with enhanced efficacy and less adverse effects has been made possible by our growing understanding of the complex neurobiological causes of depression. Patient well-being is given priority in the iterative design process, which looks into novel formulations and delivery systems. Simultaneously, standardisation efforts aid in the development of uniform assessment standards, guaranteeing a stronger and more trustworthy evaluation of antidepressant drugs. The field of antidepressant therapy is changing as a result of the continued synergy between these three pillars—design, development, and standardization—which gives hope for more individualised and efficient therapies for those with depressive illnesses. The total advancement in these fields demonstrates the commitment to raising the standard of mental health treatment globally as well as the devotion of researchers and practitioners.

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