ECRONICON OPEN ACCESS

EC PHARMACOLOGY AND TOXICOLOGY
Review Article

Drug Discovery for Suicide Management

Da-Yong Lu* and Ting-Ren Lu

School of Life Sciences, Shanghai University, Shanghai, China

***Corresponding Author:** Da-Yong Lu, School of Life Sciences, Shanghai University, Shanghai, China.

Received: September 23, 2021; **Published:** October 28, 2021

Abstract

Therapeutic drugs are now not eradicative for human suicide. The only reason for relatively small-scale drug utility in the clinic came from shortage of specific, highly effective, long-lasting and low toxicity drugs in the past. In order to promote therapeutic responses and reduce drug toxicity, neural pharmacology and pharmaceutical approaches should be introduced.

Keywords: *Antidepressants; Neural Pharmacology; Medicinal Chemistry; Human Suicide*

Backgrounds

Clinical challenge for drug design and development

Drug development for human suicide is of great pharmaceutical significances worldwide. To reduce suicide-induced human suicide, drug development is indispensable. Human suicide diagnosis currently looks simple in procedure (suicide ideation, behaviors and repeat actions). However, high-quality human suicide treatment requires a long journey (different forms of molecular diagnosis and targeting-identify from complex pathways of human depression, mania, cognitive, emotional, behaviors, persistent pain, biochemical mechanisms, neurotransmitters, gut-brain axis, viral infection, past trauma and so on). Different types of therapeutic drugs may act on different proportion of suicide patients by targeting relevant mechanisms of pathogeneses [1]. As a result, modern diagnosis, pathological pathways and molecular machinery of drugs may help treatment choice promotion and drug development revolution.

Pharmacology discipline

A number of therapeutic drugs against suicide-related pathogenesis in neurobiology and drug combination, traditional medicine, therapeutic mechanism and clinical paradigms need to be promoted. In the past two decades, we have witnessed the ups and downs in diagnostic and therapeutic transformation from psychoanalysis into neural-pharmacology. There is still no considerable progress in this sector of therapeutics transformation. This chapter reiterates the importance of genetic subject and pharmacological principle transformation in suicidal biology and drug development (gradual evolution of animal models, drug targets, mechanisms and clinical trials) and shedding new light at genetic, molecular, cellular levels in therapeutic bases-advanced drug selection systems. These patho-therapeutic relation knowledge requires the popularity of drug selection systems in the clinic.

Therapeutic categories

Therapeutics for mood disorders

Presently, licensed drugs for mood disorders (bipolar or unipolar disorders with symptoms of depression and mania) urgently require a therapeutic boost against human suicide ideation, behaviors and mortality despite a lot of neuropsychiatric study (Table 1) [2,3].

Disciplines	Different Pathways and Approaches
Pharmacology	Genetics/molecular Light or severer symptoms in the clinic Disease latency and co-morbidity
Toxicology	Doses and therapeutic terms Drug combinations
Pharmaceuticals	Long-term releasing and drug stables in blood Underlying diseases Drug formulation Herbal medicine Other types of pharmaceutical options

Table 1: *Therapeutic drug categories for mental disorder.*

The therapeutic responses and outcomes in the clinic vary significantly among different individuals. More importantly, most of chemical drugs have moderate-to-severe toxicities to patients with mood disorders. In addition, most patients will recurrent if drug treatment discontinues over half year. Thus, drug selection and development plays key role for clinical trials. Due to this therapeutic deficit, psychiatrists or physicians are more cautious in drug selection in complex clinical situation by modern diagnosis [2-5].

Diagnostics

The molecular diagnosis of mental health can be theoretically categorized into several units (genetic, molecular, cellular, circuits, physiology, behavior and patient feedbacks) [6-8]. There is no single unit that is much advantageous than the rest of other units. Modern clinician and psychiatrists should adapt to these diagnostic units and extract information from complex clinical data and symptoms (association and variation).

Patho-therapeutic relationship in neuropsychiatric study plays key role for disease treatment promotion [9-11]. Knowledge about diagnostic and therapeutic aspects of suicide prediction and prevention is accumulating. However, the different spectra of drug targets (complex chemical structures and mental illness image) promote therapeutic selection in the clinic. To update this system, neurobiological study (genotypic, phenotypic and therapeutic variability) is indispensable. So far, only limited diagnostic or therapeutic paradigms have been based on wide-range of clinical applications. Personalized medicine may be a possible way for human suicide treatment advances.

Clinical drug treatment

Many suicide ideation and events came from patient's states of depression or mania. Antidepressant or mood stabilizers are the major pharmaceutical selection for clinical patients. In clinical trials, lithium and antidepressants (especially selective serotonin reuptake inhibitors SSRIs) are most frequently utilized for major depressive syndromes and mind-stability recovery. Most mood stabilizers-including lithium may alleviate patient's manic symptoms and parts of psychiatric problems (human suicide behaviors). However, moderate-to-severe toxicities, such as hematological and carcinogenesis toxicity, especially to fetus of pregnant women were frequently reported [12]. For pregnant women, most chemotherapeutic agents or drugs should be interrupted for the health concern of both children and mothers.

Drug category

Owing to a lack of well-organized biomedical knowledge for human suicide, the drug development for neuropsychiatric disease is more based on empirical levels of doctors and symptom therapeutics against psychiatric manifestation. Only handful drugs are available

for suicide-linked prevention and treatment-an unclaimed territory for suicide knowledge overall [7]. Table 2 shows the main domain of drug categories for mental diseases (associate with different condition of human suicide).

Drug categories	Drug names	Side-effective
Tricyclic antidepressants	Amitriptyline, imipramine,domipramine, clothiepin, nortriptyline, desipramine, lofepramine	Greater
Selective serotonin reuptake inhibitors	Fluoxetine, paroxetine, citalopram, sertraline, escitalopram	Lower
Monoamine oxidase inhibitors	Phenelzine, moclobemide, tranylcypromine	Risk of drug-food interactions
Serotonin and noradrenalin reuptake inhibitors	Venlafaxine, duloxetine	Blood pressure promotion
Others	Mirtazapine, reboxetine	Over-sedate Weight-gain

Table 2: *Different types of antidepressants and pharmacological characteristics.*

Evaluative systems for drugs

The limitation of evaluative systems

To promote drug development, drug evaluative systems should be advanced by suitable animal models and high-quality biomedical assays in human cells and tissues [15,16]. In different animal models, biochemical assays, neural culture (two- or three dimensional systems), animal models (either small or big) and computational analysis (molecular-docking, *in silico*) is now widely utilized. Through different levels of experimental and clinical evaluation, the effective compounds may be identified and validated in human beings.

The biggest challenge for drug experimental evaluations and clinical applications is to transform syndrome property into genetic or molecular framework-including cerebral image, neuroscience and the utility of big animals (dogs or chimpanzees) [17]. This is a relatively novelty and medical significance in evaluative systems for suicide diagnosis and therapy. Based on this field of scientific investigations, novel therapeutic agents could be gradually developed, marketing and useful for more people in need.

Rodent models

Until now, the widest used animal models for drug evaluation are rodents (mice or rats). This breed of animal is famous for large-scale utility, uniformity in genetic background, easy to keep and low costs. However, it is relative limitation for brain anatomic division and straightforward syndrome features of psychiatric classification. In this breed of animal, cognitive or behavior information is obscure at basic psychiatric profiling.

The shortage of psychiatric features in diagnostic systems, especially intelligent levels and communication skills sabotages the quality of anti-psychiatric drug evaluation and development because intelligence destruction in small animals, like rodents is difficult to reach. Behavior observation in mice or rats is within two extremes (either the best or the worst among all animal models). Yet behavior features and psychiatry uniformity between genetic background and phenotypic outlook) is still advantageous. In this regards, some big animals may be used for other extreme evaluative system before clinical validity.

Emotional information, features and knowledge are difficult to be analyzed by rodents for size-consideration. In future study, other techniques and evaluative systems should be used for evaluating drug responses for mood disorders by rodents.

Big animals

A lot of big animals can be used for evaluating drug efficacy from variable neuropsychiatric conditions of living-bodies. Emotional and cognitive characters of big animals are proposed to be more similarity to human beings. Biological and behavior features of dogs and non-human primates is easier to be accepted than those of rodent models because their cerebral or anatomic information is comparable than cognitive, behavior and emotion in human beings [17]. The diagnostic associations between genotypic, phenotypic and emotional features will be gradually translated into human mental health knowledge and therapeutic paradigms after evaluation in large animals.

In vitro pharmacological evaluation

In the past, *in vitro* evaluative models (neural cell or tissue culture) exhibits closer association in genetic and molecular knowledge enrichment and accumulation. It can save a lot of costs and times. It is the main avenue for neurobiological study.

Brain cell and stem study improved greatly for techniques and medicine in the past four decades. Among these cutting-edge techniques, fluorescence- or isotope-labeled molecules in living brain cells or tissue cultures promote biochemical exploration and pharmaceutical updating.

Bioassays

Biochemical or molecular mechanistic study is the major pathway for neuropsychiatric and psychopharmacology researches. The understanding of human suicide and drug targeting is based on both drug responses and mechanisms. Thus, increasing identification of biochemical or molecular biomarkers is greatly useful for neuropathology diagnosis and high-quality drug developments [18]. Major therapeutic pathways, targets and mechanisms are enlisted in the table 3. These wealth of biochemical information will impacts therapeutic outcomes in the clinical trials. These bioassays are mostly compared with antioxidants, inflammatory, neurotoxicity and others.

Neural	Targeted pathways	Effectors
Ion channel	Na, K, Ca	Mg, Mn
Transmitters	Monoamine	Serotonin, dopamine
Synapse activity	Receptor, enzyme, reuptake	Neural function
Signal receptors	5-HT1A receptor	Neural impulsive and functional
Genes	MRP1, BCRP	Genotypic, SNP, Copy number
Molecule	Tau, β-amyloid peptide	Neural lesion and degeneration
Cerebral	Amygdala, hippocampal, striatum	Aversion, anxiety and depression
Neurons	Damage or degeneration	Eye ball or facial movement changes
Psychiatric diseases	Cognitive, behavior or emotion	Schizophrenia, depression

Table 3: *Biological pathways for neural function associated with suicide risks.*

Human genetics

Two main parts of genomic techniques widely use in clinical studies (genetic alteration and genome-wide association studies) [13,14]; different genetic or genomic technology, such as microarray and genomic sequencing is popular now. New technology, such as genomic editing may gradually update gene diagnosis and therapy.

Different drug targets and pathways

General outlook

Due to the shortage of drug targets associated with human suicide, some potential pharmacological pathways and targets are proposed [18] (Table 3). From these pharmacological pathways and targets, neurobiological and pharmaceutical information, knowledge, diagnosis and therapeutics should be updated and categorized.

Ion channels

K^+, Na^+, Ca^{++} and Cl^- are major ionic elements for translating neuron impulses into human behaviors, which connect and balance brain information and function through regulation of cellular membranes integrity, ion transporters, drug targets and therapeutic responses in human central nerve system. A lot of advanced explorations have been emphasized on drug development in human neural and central nerve systems.

Neurotransmitters

The generation, regulation and degradation of neurotransmitters in synapses play key roles in neuropsychiatric functions and symptoms. Shortage or over-production of different kinds of neurotransmitters (chemical, biological or peptides) and their receptors may lead to a variation in brain pathology, functions, psychiatric symptom and behaviors (Chapter 4). This type of biological pathway and network warrant a half numbers of drug licensing in the pharmaceutical markets for central nerve system diseases (CNS agents).

Signal transduction

Signal transduction and circuits with genes and molecules is complex biological processes and systems in the clinic. The interactive and crosstalk machinery of neurons and stem tissues in human brains (central nerve system) and human digestive systems (brain-gut axis) are major pharmaceutical targets and mechanisms in drug discovery, evaluation and validation in the clinic worldwide.

Dysfunctional proteins, polymers and enzymes

Dysfunctional proteins, polymers, enzymes undermine the structures, repair, regulation and function of human brains and possibly trigger a sequential of pathological pathways in central nerve system. Many abnormal proteins and polymers, such as Tau or β-amyloids can be found in cerebral areas of animals or patients with mental disorders, especially neurodegenerative diseases. Some therapeutic agents are effective against these pathological molecules, pathways and damages that are expected to function with psychiatric symptoms and human suicide.

Genotypic and phenotypic insights and targets

Genotypic and phenotypic features for human neurobiology determine almost all neural activity, function and connection in human bodies. There are approximately 400 - 1000 active human genes participating partly for different mental diseases. Until now, SNP, sequencing and copy-numbers are favorable techniques for identifying neuropathy and psychiatric diseases. Drug targets on these genes, molecules, pathways and network affect CNS disease advances and drug developments [4,5].

GWAS for testing neuropsychiatric disorders is the most promising trend in the past reports. Different mental diseases show different associated genes and molecules. The known and unknown genetic alteration of mental diseases has been categorized in table 3.

Proved mental disorders

Schizophrenia; bipolar and autism spectrum disorders.

Under-investigation

Major depressive disorder (MDD); Attention deficit hyperactivity disorder (ADHD); obsessive-compulsive disorder (OCD); post-traumatic stress disorder (PTSD); Tourette disorder.

The greatest obstacle for neuropsychiatric studies is the boundary and overlapping of current disease dimension in diagnosis and therapeutics. Without clear boundary of mental diseases, patients may be over-treated or under-treated. The genetic study of this issue may solve this vexing problem in a greater pace and width [14].

Gene therapy

Gene treatment shows promising therapeutics against neuropathy in psychiatric patients [19]. It is shown that manipulates UBE3A gene can counteract with CNS deficit in the clinic. Other gene therapy is recommended for human epileptic and autoimmune diseases.

Molecular docking

More recently, experimental drug evaluations need greater amount of money (modern instruments, biochemical reagents, different animals and staff salary). Increasing money investment will lead to greater economic burden and losses for pharmaceutical companies and patients needing drug treatments. To face with economic burden, molecular-docking (computational analysis of drug activity, interaction and configuration-*in silico*) have been increasingly applied in drug design and early evaluation.

Many molecular structures of human beings have been projected in computers and prediction of potential efficacy of known chemical compounds and drugs. Preliminary mathematical/computational drug evaluations open a door for molecular analysis with reasonable cost. Molecular docking (computational analysis and theoretic building) is no longer a topic of basic study. It plays increasing roles in drug designs and researches. Comparison of activity of new drug targets, molecular conformation and pathological pathways is one of the major pharmaceutical strides in drug development since this millennium.

Herbal medicine

Drug development for prevention of human suicide can be improved by combining herbal medicine with the prescribed medicine [20-26]. As mentioned above, many chemotherapeutic agents for neuropsychiatric diseases are toxic after long-term utility. Drug toxicity is a serious drawback for anti-psychiatric agents and drugs in the clinic. Across history, many Asia therapies still use herbal medicine for which some undesired side-effects may be avoided. In addition, therapeutic costs may be reduced by avoiding extracting processes in drug production.

Drug combination

Evaluation and comparison

Drug combination is a usual therapeutic paradigm for many refractory diseases, such as HIV [27-29] and cancer [30,31]. May drug combinations increase the chances of suicide prevention and treatments? Previously, drug combination for mental illness was not to be fully understood. From early literature, it was discovered that drug combinations would show higher therapeutic-index than single drug treatment if it was optimized. Because drug dosages and plasma concentrations of combined drugs could be lower than those of single drugs. How to optimize drug doses and responses by drug combination is an challenging topic for the future. As usual, hidden rules and principles behind paradigms against suicide should be translated from past experience of drug selection into decision-making by guided strategies.

Mathematic equations

Drug combination can lead to either better or bad therapeutic outcomes in the clinic. It needs good principle to guide because complete evaluating every possibility of drug combination is more convincing than other strategies at this stage. No definite models or bioassay have been followed until now. More mathematical or computational evaluation may be helpful [32,33]. Currently, explorative efforts can be covered by mathematical possibility (enormous number) for a single dimension of mental disorder (Equation 1 and 2). For example, approximately 30 drugs have been utilized for psychiatric disorder treatments (Table 2). We can approximately estimate the total numbers of all combination:

Two drug combination for single mental diseases:

$C=30\times29/1\times2=435$ (Equation 1)

Three drug combination:

$C=30\times29\times\times28/1\times2\times3=4060$ (Equation 2)

All drug combination (A) for most mental diseases (N):

$A = C \times N$ (Equation 3).

In summary, many drug combination studies should be undertaken to safeguard the quality of drug combination in the clinic.

Mathematical modality

Formerly, neural image observation was based on 3-dimentional data of human brains. It was not very informative for neuropsychiatric variation. By introducing mathematic models (integrable (3+1) dimensional system), these shortcoming may be overcome [34]. This changeable system could be molecular information, drug response or spectral shifting. Further work of mathematic and experiment is needed.

Cost-effective considerations

Since suicide treatments may last very long, cost-effective consideration in clinical trials is an inevitable pathway [35]. This issue might be complex because patients commonly use one or two drugs in long term. The pharmaceutical companies should reduce drug costs for every patient by principle of drug selection and diagnosis advances. To reduce therapeutic costs, drug developmental system and high-quality drug selection should be optimized.

Discussion

The biggest difference and similarity between suicide and mental illness should be discovered by optimizing diagnostic and therapeutic systems at genetic- and molecular levels. How to explore the relationship between symptom and genetic variation is a great challenge. We speculate that genetic or molecular evidence for suicide risks and therapeutics should be implemented in broader-range, less toxicity and long-term utility.

Presently, different types of therapeutic drugs own their territories for mental diseases. Symptom-easing agents or drugs like mood stabilizers or antidepressants are widely depended nowadays. Some types of antidepressants, such as SSRI (selective serotonin reuptake inhibitors) are relatively cheap and more effective than other types of antidepressants. However, a body of clinical literatures showed that SSRIs could induce suicide ideations and behaviors in depressed patients, especially in children [36-40]. Lately, human genetic predispo-

sition is proposed for suicide emergence and behaviors [39]. It became complicated now. Further exploration for pathological pathways and progresses should be focused on system widening and high-efficiency [41-45].

Future Perspectives

Figure 1 represents the outlook of drug developments and licensing for suicide treatment.

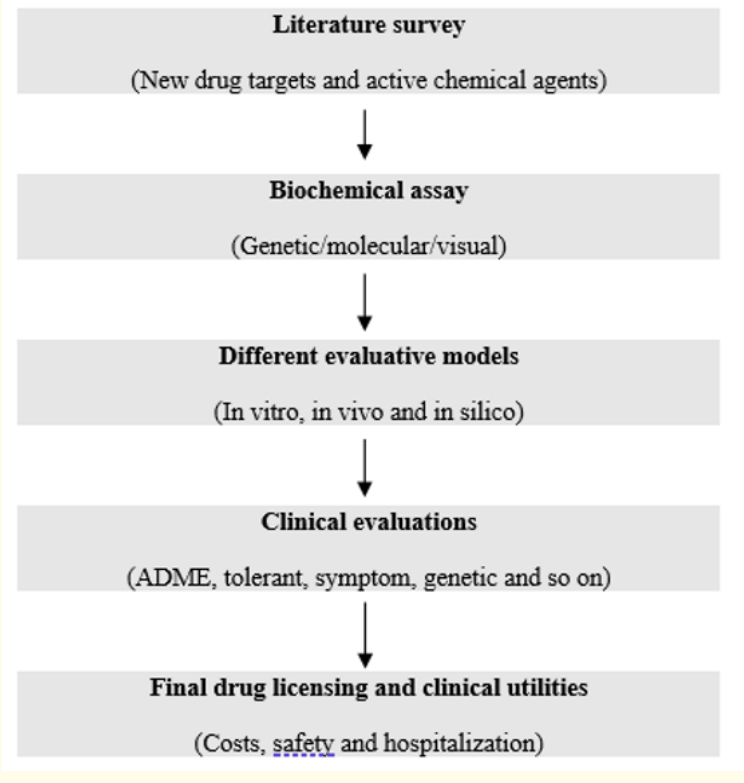

***Figure 1**: A roadmap of suicide/mental illness drug developments.*

In the future, drug development chain for suicide will face great changes. Yet, etiologic as well as pathogenic study is the foundation [36-45]. In the near future, gene therapy and herbal medicine will be possible for therapeutic gains (high efficacy, low toxicity and long-term usefulness) in the clinic.

Conclusion

Clinical drug treatment is an easiest therapeutic option for most diseases. Yet drug therapeutics for suicide/mental illnesses is a great challenge because many pathologic causalities and pathways have not been fully understood at genetic or molecular levels. Owing to this setback of diagnostics, we should focus on genetic or molecular exploration in a long period of times.

Bibliography

1. Marshall M. "Roots of mental illness". *Nature* 581 (2020): 19-21.

2. McAllister-Williams R and Ferrier IN. "Pharmacological management of bipolar affective disorder". *Psychiatry* 8.6 (2009): 120-124.

3. McAllister-Williams R and Ferrier IN. "Pharmacological management of unipolar affective disorder". *Psychiatry* 8.4 (2009): 113-119.

4. Lu DY., *et al*. "Genetics and bioinformatics studies of antidepressant drug therapeutic efficacies and toxicities, a current overview". *Recent Patents on CNS Drug Discovery* 9.3 (2014): 193-199.

5. Lu DY., *et al*. "The efficacies and toxicities of antidepressant drugs in clinics, building the relationship between Chemo-Genetics and Socio-Environments". *Central Nervous System Agents in Medicinal Chemistry* 16.1 (2016): 12-18.

6. Lu DY., *et al*. "Genetics and bioinformatics study of antidepressant drugs, recent advancements and future trends". Suicidal Ideation: Predictors, Prevalence and Prevention. Edition. Bradley Weaver. Nova Science Publishing. US 3 (2015): 57-71.

7. Lu DY. "Suicide Risks and Treatments, New Ideas and Future Perspectives". Edition Da-Yong Lu, Nova Science Publishers (2017).

8. Serafini G., *et al*. "Suicidal ideation: a comprehensive overview". Suicidal Ideation: Predictors, Prevalence and Prevention. Edition. Bradley Weaver. Nova Science Publishing. US 1 (2015): 1-42.

9. Lu DY., *et al*. "High quality treatments for human suicidal events and mortality". *Advanced Techniques in Biology and Medicine* 8.2 (2020): 269.

10. Mandowr RA. "Antidepressants medication and the risk of suicide attempt". *Toxicology International* 19.1 (2012): 42-46.

11. Lucas G. "Fast-acting antidepressants: are we nearly there". *Expert Review of Neurotherapeutics* 8.1 (2008): 1-3.

12. Lu DY and Lu TR. "Drug treatments for human suicide". *EC Pharmacology and Toxicology* 8.9 (2020).

13. Malhotra D and Sebat J. "CNVs: harbingers of a rare variant revolution in psychiatric genetics". *Cell* 148 (2012): 1223-1241.

14. Krystal JH and State MW. "Psychiatric disorders: diagnosis to therapy". *Cell* 157 (2014): 201-214.

15. Menchetti M., *et al*. "Depression in primary care: Interpersonal counseling vs selective serotonin reuptake inhibitors. The DEPICS study. A multicenter randomized controlled trial. Rationale and design". *BMC Psychiatry* 10 (2010): 97.

16. Menchetti M., *et al*. "Moderators of remission with interpersonal counseling or drug treatment in primary care patients with depression: randomized controlled trial". *British Journal of Psychiatry* 204.2 (2014): 144-150.

17. Grimm D and Louisiana K. "Chimpanzee sanctuaries open door to more research". *Science* 353.6298 (): 433-434.

18. Lu DY., *et al*. "Suicide risks and prevention, neuropathogenic study". *EDEWEISS: Psychiatry* 4.1 (2020): 124.

19. Ashraf GM. "Gene therapy for neuroprotection and neurorestoration (Part I)". *Current Gene Therapy* 19.6 (2019): 358.

20. Lu DY and Lu TR. "Drug discoveries from natural resources". *Journal of Primary Health Care and General Practice* 3.1 (2019): 28.

21. Lu DY and Lu TR. "Herbal medicine in new era". *Hospice and Palliative Medicine International Journal* 3.4 (2019): 125-130.

22. Rehman S and Ray A. "Neuroprotective medicinal plants, focus on Curcuma longa". *EC Pharmacology and Toxicology* 8.8 (2020): 16-23.

23. Parasuraman S. "Herbal drug discovery: challenges and perspectives". *Current Pharmacogenetics Personalized Medicine* 16.1 (2018): 63-68.

24. Putta S., *et al*. "Anthocyanins: Possible role as multitarget therapeutic agents for prevention and therapy of chronic diseases". *Current Pharmaceutical Design* 23.30 (2017): 4475-4483.

25. Tian LM., *et al*. "Metabolism of anthocyanins and consequent effects on the gut microbiota". *Critical Review in Food Science and Nutrition* (2018): 1533517.

26. Rajput R., *et al*. "Efonidipine exerts cerebroprotective effect by down-regulation of TGF-β/SMADt signaling pathway in diabetic-2-dependan rats". *Journal of Molecular Neuroscience* 71.9 (2021): 1884-1896.

27. Lu DY., *et al*. "New perspectives of HIV/AIDS therapy study". *Recent Patents on Anti-infective Drug Discovery* 9.2 (2014): 112-120.

28. Lu DY., *et al*. "HAART in HIV/AIDS treatments, future trends". *Infectious Disorders-Drug Targets* 18.1 (2018): 15-22.

29. Lu DY., *et al*. "HIV/AIDS curable study, new forms of therapeutic trinity". *Recent Patents on Anti-Infective Drug Discovery* 13.3 (2018): 217-227.

30. Lu DY., *et al*. "Anticancer drug combinations, studies from different pathways". *Cell and Developmental Biology* 4 (2015): 166.

31. Lu DY., *et al*. "Anticancer drug combinations, studies for all possibilities". *Advances in Pharmacoepidemiology and Drug Safety* 5 (2016): e138.

32. Lu DY., *et al*. "Anticancer drug combination, how far we can go through?" *Anti-Cancer Agents in Medicinal Chemistry* 17.1 (2017): 21-28.

33. Lu DY., *et al*. "Drug combination in clinical cancer treatment". *Reviews on Recent Clinical Trials* 12.3 (2017): 202-211.

34. Sergyeyev A. "Integrable (3+ 1)-dimensional system with an algebraic Lax pair". *Letters in Mathematical Physics* 108.2 (2018): 359-376.

35. Patel A. "The cost of mood disorders". *Psychiatry* 8.2 (2009): 76-80.

36. Rubino A., *et al*. "Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: retrospective cohort study". *British Medical Journal* 334.7587 (2007): 242-247.

37. Kovacs D., *et al*. "Antidepressant treatment response is modulated by genetic and environmental factors and their interactions". *Annals General Psychiatry* 13.1 (2014): 17.

38. Teicher MH., *et al*. "Emergence of intense suicidal preoccupation during fluoxetine treatment". *The American Journal of Psychiatry* 147 (1990): 207-210.

39. Lu DY., *et al*. "May genetic factors play a role in the risk of antidepressant-induced suicide". *Medical Hypotheses* 69.6 (2007): 1380-1381.

40. Lu DY., *et al*. "The suicidal risks and treatments, seek medications from multi-disciplinary". *Central Nervous System Agents in Medicinal Chemistry* 16.3 (2016): 231-239.

41. Posner K., *et al*. "Columbia Classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDAS pediatric suicidal risk analysis of antidepressants". *The American Journal of Psychiatry* 164 (2007): 1035-1043.

42. Souza HY., *et al*. "Use of ketamine in depressive episodes resistant treatment: effectiveness data and perspectives in clinical practice". *EC Pharmacology and Toxicology* 8.8 (2020): 2-15.

43. Lu DY., *et al*. "Pathology study for human suicide". *Health and Primary Care* 5 (2021): 1-4.

44. Orsolini L., *et al*. "Understanding the complex of suicide in depression: from research to clinics". *Psychiatry Investigation* 17.3 (2020): 207-221.

45. Lu DY., *et al*. "Human suicide study, new insights and drug development". *Indian Journal of Community Medicine* 3.1 (2020): 1028.

Volume 9 Issue 11 November 2021