Drug Repurposing Approaches for Depression: Rationale and its Clinical Experience

Mimansa Kandhwal[1], iD Amarjot Kaur Grewal[2*], iD Varinder Singh[3], iD Heena Khan[4] iD and Thakur Gurjeet Singh[5] iD

[1,2,3,4,5]*Chitkara College of Pharmacy, Chitkara University, Punjab, 140401, India*

*amarjot.kaur@chitkara.edu.in (Corresponding Author)

ARTICLE INFORMATION

ABSTRACT

Background: Drug discovery is a very time-consuming, tedious, and expensive process lasting for about two or more decades. This complexity of the process of drug discovery and the sluggish pace at which new drugs are being discovered draw the attention of scientists to redefine the whole process with the help of drug repurposing. The usage of old drug moieties in any other disorder with all new mechanisms is defined as repurposing. Repurposing of drugs knocks out the pre-clinical phase and related studies to give that molecule a redefined purpose. Data from these studies may be used in discovering newer molecules to save human effort, time, and expenses as well.

Purpose: The complex etiology of depression and resistance to its treatment drive novel discoveries via therapeutic repurposing and pharmacological repositioning to treat this complex disorder. In addition to the reduction of neurotransmitters such as epinephrine and serotonin, additional processes like inflammation, inadequate blood flow, and neurotoxicants are also being examined as possibly implicated mechanisms.

Methods: Data was extensively collected, thoroughly reviewed and analysed from research published in the respective field.

Results: Taking into consideration the aforementioned pathways has led to the development of repurposed drugs that can be used to treat treatment-resistant depression (TRD).

Conclusions: The incorporation of artificial intelligence in drug repurposing may also enhance the chances of its success rate as it deals with data digitalization which is the main core mechanism used in drug repurposing.

1. Introduction

Major Depressive Disorder has been spreading within the human race impacting the population worldwide. The World Health Organization (WHO) in their recent survey in March 2023 claims that around 3.8% of people are suffering from depression all around the globe. Out of which 5.7% of the population is above 60 years and 5% are adults. Women are more prone to develop depressive symptoms than men. In the same data, it was also verified that in the adult population, 4% are men and 6% are women. A total of 280 million people in the world are already suffering from major depressive disorder (MDD) (Institute of Health Metrics and Evaluation, 2023). The fact that up to two-thirds of depressed people do not react to first-line antidepressants demonstrates the need of developing new medicines that target a wide variety of targets or novel targets. People who suffer from depression often experience severe sadness, anxiety, thoughts of suicide, and cycles of mania and depression, a condition known as bipolar depression(Little

2009, Cain 2007). Depression was ultimately brought on by both hereditary and epigenetic causes. Late-life depression, also known as vascular depression, is a condition that mostly affects the older population. Because late-life depression is associated with vascular diseases and inflammation, this finding suggests that improving blood circulation and reducing inflammation may help treat it (Hamilton 1960, Kupfer 2005). Deficits in the neurotransmitters noradrenaline (NA) and serotonin (5HT) have been associated with major depressive disorder (MDD) for many years, namely in the hippocampus and the prefrontal cortex. Antidepressants that prevented the neuronal absorption of catecholamines were shown to be effective in treating depression, whereas medicines like reserpine, which depleted catecholamines, produced depression. However, there is mounting evidence that dopamine, glutamate, and gamma-aminobutyric acid play important roles in both the development of MDD and its treatment (Schildkraut 1965,& Taylor, Fricker, Devi & Gomes 2005). In addition, MDD and antidepressant responsiveness are both associated

with stress as well as disruption of the hypothalamic-pituitary-adrenal axis (Kinlein, Wilson, & Karatsoreos 2015, & Rodriguez, Monsalves-Alvarez, Henriquez, Llanos, & Troncoso, 2016). The stress hormone cortisol is high in the bodily fluids of depressed people (Holsboer 2001, Pariante 2017). The antidepressant mifepristone, which is a glucocorticoid receptor antagonist, has been investigated for its effect on depression (Howland 2013). The stimulation of melatonin receptors could be therapeutic for depression (K. Pytkaet al., 2017). Patients suffering from MDD may see an improvement in their mood when they take the antidepressant agomelatine because it stimulates G-protein-coupled melatonin receptors 1 and 2 (Gahr 2014). The antidepressant pharmaceutical aprepitant, which blocks neurokinin 1 receptors, was reported to show promise as a possible therapy for major depressive disorder (MDD) in early clinical research; nevertheless, the medication was not licensed for use in treating MDD owing to its poor efficacy in doing so (M. Keller et al., 2006). These deficiencies in drug discovery are a primary cause for the research and development of novel antidepressant medications.

The making of a brand-new medication is an extremely laborious and time-consuming operation. Some medications are not successful in the preclinical testing phase despite several years of diligent labor and patient waiting, which results in a significant amount of wasted time, money, and effort. Drug repurposing is a method that researchers are looking at as a possible shortcut to the production of new pharmaceuticals in a shorter amount of time. This is because researchers are always working to produce new medications for depression and have a strong desire to do so. As its name suggests, the process of repurposing pharmaceuticals entails assigning an existing medication a whole new objective or role in the body. Some researchers have separated the idea of repurposing into two distinct subcategories: "reformulation," which refers to the process of developing a new formulation for the same drug, and "repositioning," which refers to the process of identifying a new therapeutic use for a drug that has already been discovered (S. Pushpakomet al., 2019). Both of these subcategories fall under the umbrella term of "repurposing." The repurposing drug is a method that is seen as a way to rediscover value in "old molecules" and find new therapeutic applications, particularly in fields that have a high risk of failure, such as depression (Y Cha et al., 2018). One could argue that the phrase "repositioning" is the only one that is closely related to "repurposing." It is seen as a strategy that may save expenses while at the same time lowering the risk involved. Having already assessed whether or not a substance is acceptable in terms of its safety and tolerability lowers the risks involved with future development. This article is a discussion on the goals and significance of repurposing medications concerning depression.

2. History and Relevance of Repurposing of Drugs

In the research history drug repurposing was coas a serendipitous event such as the discovery of sildenafil (used in angina) in erectile dysfunction was the first discovery that grabs the attention of scientists in 2000. Whenever any drug molecule exhibited any off-target therapeutic effect it catches the attention to be utilized commercially (Osterloh 2004). The treatment of morning sickness with thalidomide was refocused on multiple myeloma (A. Palumbo et al., 2008). The achievement sparked a significant amount of interest in repurposing, which ultimately led to the establishment of a great deal of new repurposing businesses concentrated on new business ventures. Repurposing has a substantial part in the life cycle management of goods with an R&D cost of 10–50%, according to several studies as well as findings of market research (A. Palumbo et al., 2008). Baker and coworkers presented a bibliometric study in which they investigated many medications in more detail to get a better understanding of the background behind the breadth of the practice of drug repurposing (Baker, Ekins, Williams, &Tropsha, 2018). A few examples include the synthesis of chlorpromazine in the 1950s, which was earlier employed in the control of psychic disorders and as a preoperative medication. Chlorpromazine was later on experimented for treating several disorders, such as viral cold and cough, and several symptoms which are exhibited in patients suffering from cancer (radiation therapy) (Abbruzzese, Matteoni, Persico, Villani, &Paggi, 2020). An antimalarial chemical known as chloroquine was first created in the year 1934. Subsequently, before 1960, it was used to treat a wide variety of disorders, including parasite infections, fever, and skin rashes caused by lupus but it is proposed to be remodeled for its use in the global pandemic COVID-19 (Tripathy, Dassarma, Roy, Chabalala, &Matsabisa, 2020).

Developing drugs via traditional methods is a very time-consuming and inefficient procedure. These costs are only going to continue to rise, even though the number of drugs that are approved each year relative to the amount of money spent on development has remained relatively constant or has even decreased for the majority of the past decade (Law, Tisoncik-Go, Korth, &Katze, 2013). The process of transforming a molecule into a drug and bringing it to the bedside of a patient takes approximately ten to fifteen years and costs approximately two to three billion dollars. Repurposing of existing pharmaceuticals, which may refer to medications that have already been authorized or are in the process of being created for any illness, is a distinct strategy that tries to sidestep the earliest phases of drug development (the preclinical phase and safety studies in humans). Repurposing existing pharmaceuticals can

refer to drugs that have already been permitted or are in the process of being produced for any ailment. According to research done by Nosengo 2016, it was estimated that the process of repositioning a medication would take around 6.5 years and cost an average of 300 million dollars (Nosengo 2016). It is interesting to note that the first medicine to be reported to have antidepressant effects was iproniazid. Iproniazid was a chemical that was initially developed to treat tuberculosis and exhibited "side effects" of euphoria, psycho-stimulation, increased hunger, and enhance sleep (Hillhouse & Porter, 2015). It is interesting to note that iproniazide was the first medicine to be reported to have antidepressant effects. In the absence of serendipity, repurposing may be guided by a variety of scientific data, such as in vitro cellular testing, animal models, or markers of sickness in populations that have been affected.

In other words, the process may be driven, for instance, genes that are already established as having a connection to a disease may be used in the process of locating possible pharmacological targets (Zheng, Sun, & Simeonov 2018). Upjohn chemists in the 1960s discovered that topical hair growth was the primary adverse effect that occurred following treatment with minoxidil as an anti-hypertensive medication. Androgenetic alopecia is now treated with topical minoxidil, which is considered the "gold standard" treatment (Bryan 2011). Having previously proven the safety and tolerability of a chemical lowers the risks involved with further development, making this method not only cost-effective but also risk-free. When developing new pharmaceuticals, there is always the possibility that the whole project will be a bust, which will, in turn, result in more financial losses and the loss of valuable time.
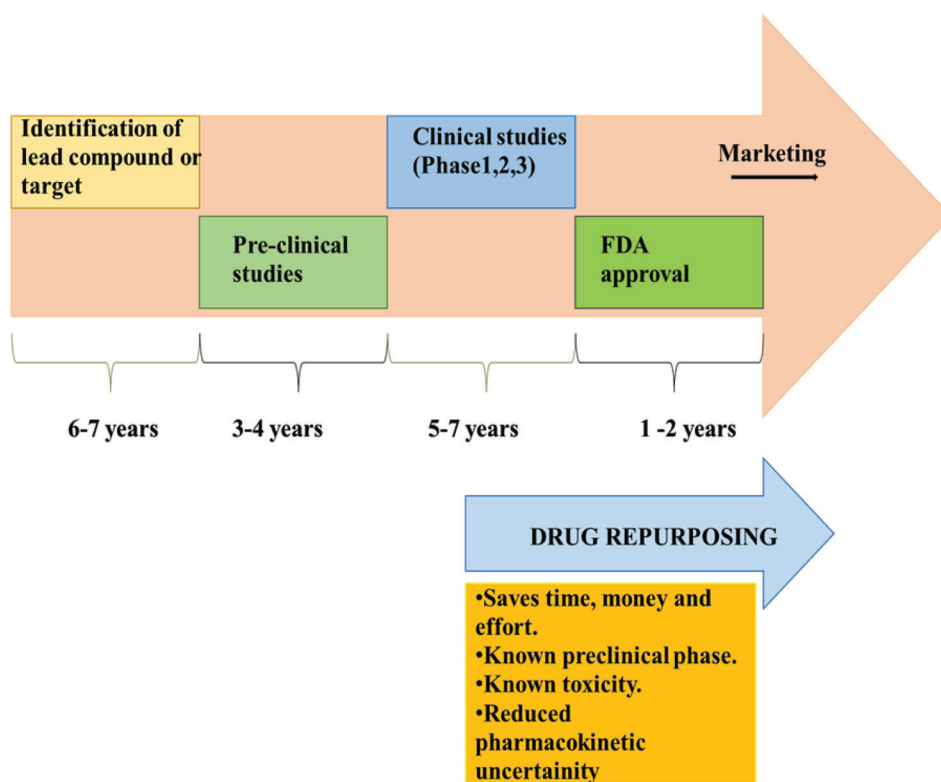
Figure 1: Depiction of the relevance of drug repurposing concerning time, pharmacokinetic profile, human effort, and capital used in the relative studies.
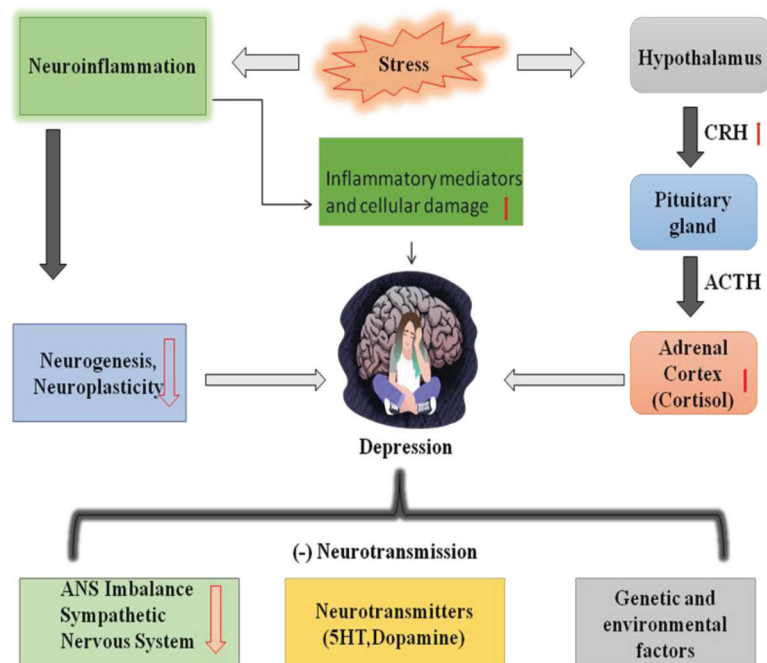
3. Pathophysiology and Management of Depression

3.1. Pathophysiology of Depression

Several factors are responsible for the progression of depression. Different researchers proposed different hypotheses that could be an underlying factor in disease progression. One of the major theories of depression is the monoamine theory (Delgado 2000). Alleviated levels of monoamines such as serotonin, norepinephrine, and dopamine in the brain could lead to the progression of this disorder. In the field of research on depression, serotonin has received the greatest attention (J. H. Meyer et al., 2006 & Goldberg, Bell Jr, & Pollard, 2014). Studies that used tryptophan depletion, which lowered central serotonin synthesis, provide the most direct evidence for

an abnormally reduced function of the central serotonergic system (Dell'Osso, Carmassi, Mucci, &Marazziti, 2016 & Tsao, Lin, Chen, Bai, & Wu, 2006). Tryptophan depletion was used since it was shown to limit the synthesis of serotonin in the central nervous system. Such a reduction leads to the development of depressive symptoms in subjects who are at an increased risk of depression (subjects with MDD that are in full remission, healthy subjects who have a family history of depression) which may be mediated by an increased rate of brain metabolism in the ventromedial prefrontal cortex and subcortical brain regions (Coppen, Shaw, Herzberg, &Maggs, 1967, Neumeister 2003 & Cowen, Parry-Billings, &Newsholme, 1989).Apart from the monoamine brain-derived neurotrophic factors(BDNF) are also responsible for depression progression. The growth of Neurons present in the brain and monoaminergic neurons is linked with the BDNF (Martinowich, Manji, & Lu, 2007 & Prabhakar, Khan, Grewal, & Singh, 2022). It is responsible for the

survival and functioning of adult neurons (Rihal, Kaur, Singh, & Abdel-Daim, 2022). Reduction in the levels of BDNF because of several factors such as stress, and anxiety may lead to atrophy in the hippocampus area and reduce the functioning of monoaminergic neurons which act as a protective shield against any CNS disorder (Khan, Bangar, Grewal, Bansal, & Singh, 2022, Brunoni, Lopes, &Fregni, 2008, &T. Yang et al., 2020). This alleviation in the levels of BDNF may also allow the hippocampus to lose its ability to inhibit CRF(corticosteroid-releasing factor) release which ultimately increases the levels of glucocorticoids in the brain (A. Moussaieff 2012). Glucocorticoids are increased when the human body is exposed to persistent stress and anxiety. Increased levels of cortisol during stress and the inability of the hippocampus to inhibit CRF (Herbert 2013). Apart from this dysregulation in the HPA (Hypothalamus pituitary axis) axis due to stress may also lead to increased release in CRF leading to depression (Barden 2004, &Plotsky, Owens, &Nemeroff, 1998).

Figure 2: Diagrammatic Representation of Pathophysiology of Depression.

3.1.1. *Management of Depression*

There are two or three primary treatment options available to manage a patient who has been diagnosed with MDD. These choices include psychotherapy, medication, and somatic therapies. The combination of psychotherapy and medication may be beneficial for patients whose depression ranges from mild to severe (C. Otte et al., 2016). Treatment-resistant

drugs (TRDs) are a very common problem in managing depressed patients. In the case of a patient suffering from just moderate depression, the treatment may first consist of psychotherapy, and then, if necessary, a move to medication might be made after a few weeks (Souery, Papakostas, & Trivedi, 2006). There are a variety of factors that might influence mental health, including physical activity and exercise, balanced food habits, better sleep patterns, and

others. In addition to these treatments, psychotherapies are also an essential component of depression treatment. Such therapies include cognitive-behavioral therapy, behavioral activation treatment, and interpersonal psychotherapy (Mann 2005). On the other hand, antidepressant medicines are much more successful in treating severe types of depression illness because they have a more quick beginning of the action. In addition, to avoid a return of the condition, psychotherapy is often recommended for patients who have responded well to antidepressant treatment. In general, it has been shown that combining the two treatments produces better results than using each one alone (Dowrick 2009). These medications consist of serotonin-norepinephrine reuptake inhibitors also referred to as SNRIs which further are classified into two subgroups known as selective serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants (TCAs), 5-HT2 receptor modulators, tetracyclic and unicyclic antidepressants, and monoamine oxidase inhibitors (MAOIs). The sixth category includes a variety of antidepressant medications, such as tianeptine (a major methyl donor that is required for the synthesis of several neurotransmitters), reboxetine (a selective inhibitor of norepinephrine reuptake), agomelatine (an agonist for melatonin (MT1 and MT2) and serotonin (5-HT2C) receptors), ademetionine and Agmatine (Cuijpers, Reynolds III, Donker, Li, Andersson, & Beekman, 2012, Weilburg 2004, & D. Brent et al., 2008). Agmatine is a selective inhibitor of the NMDA receptor while on the other hand ademetionine is a chief donor of a methyl group, further required for the production of major neurotransmitters (Freitas, Neis, & Rodrigues, 2016). Due to depression's complex etiology, conventional drugs for the disease possess multiple ill effects (libido loss, dyspepsia, pain), protracted therapeutic rate, bad recovery, insignificant remission, and low response rates, there is a dire need for the development of new molecules in depression and drug repurposing is a promising approach towards new drug development.

4. Clinical Perspective of Repurposing of Drugs in Depression

4.1. Clinical Applications

Most projects fail because of unforeseen clinical side effects and tolerability, unrelated to therapeutic hypotheses. To improve effectiveness and lower medication development costs, the traditional approach must be modified to reduce compound rejection rates. Drug repurposing boosts efficiency. Drug repurposing usually begins with molecules that have passed human safety and tolerability tests. Compounds are then employed for unintended medicinal conditions. Thus, preclinical toxicity doesn't hinder development. Clinical

studies assessing the efficacy and new purposes for older drugs possible will be identified in several ways. Although this occurs seldom, clinical monitoring in one environment may sometimes show an additional advantage that was not planned. Basic discovery research conducted for a specific medical illness complication may, through a different route, show that the molecular target of a particular molecule also plays a function in a condition that was not the primary rationale for the study. For instance, AZD0530's target, Fyn kinase, is implicated in the process of Alzheimer's disease as well as in the growth of solid tumor cells (Nygaard, van Dyck, &Strittmatter, 2014). This broadens AZD0530's potential utility, as it might be used to treat a wider variety of diseases. There is also the possibility that a specific molecule may function through previously undiscovered targets that are connected with various disease states. Because of this, a significant number of academic drug discovery programs begin the process of treatment development by looking for compounds that have been authorized by the Food and Drug Administration of the United States that target other molecules (Hughes, Rees, Kalindjian, & Philpott, 2011). For instance, a study that was conducted almost a decade ago and was funded by the United States National Institutes of Health (NIH) identified the action of antibacterial cephalosporins in regulating glutamate transporters (J. D. Rothstein et al., 2005). This led to the development of a therapeutic trial of ceftriaxone for amyotrophic lateral sclerosis, which was eventually terminated due to a lack of efficacy (ClinicalTrials.gov NCT00349622).

4.2. Repurposed Drugs in Depression

Numerous repurposed medicines for depression are now being researched or have been granted permission by the USFDA for use in clinical settings from a variety of pharmacological categories. These categories include medications that are related to the central nervous system (CNS), such as second-generation (atypical) antipsychotics (McGirr, Vöhringer, Ghaemi, Lam, &Yatham, 2016), NMDA receptor antagonists and anesthetics, GABA receptor modulators, agonists for dopamine, anticholinergic drugs, drugs which can stimulate CNS, antiepileptic agents, drugs used in allergies (histamine antagonists), and ergot derivatives, as well as medications that are not related to the CNS, such as thyroid products, antidiabetic agents (Ebada 2017). Because of the pharmacological category they fall within, these medicines trigger their antidepressant effects through a variety of different mechanisms. Table 1 contains a comprehensive listing of repurposed medications for MDD along with information on their mechanisms of action, notable side effects, contraindications, and doses.

In addition, a summary of relevant repurposed drugs that can be used in depression can be found in Table 1. and miscellaneous drugs that are repurposed from their conventional usage to some other proposed disorder are mentioned in Table 2.

Table 1: Repurposed and conventional Pharmacological profile of repurposed drugs used in Depression.

Sr. No	Drug	Brand name	Proposed Mechanism of Action	Conventional Use	Reference
1.	Ketamine	Ketalar®	Activation of AMPA receptor	Anesthetic agent	(Potter & Choudhury2014)
2.	Metformin	Glucophage, Riomet®	Improves cognitive function	Type 2 Diabetes	(C. C. Zhang *et al.*, 2020)
3.	Scopolamine	Maldemar® and Scopace®.	Activation of AMPA receptors & m TOR signalling	Anticholinergic drug	(A. E Martin *et al.*, 2017)
4.	Valproic acid	Belvo®.	PI3K/Akt/mTOR activation (cell survival)	Anti-epileptic drug	(Gurpur, Liu, Burkin, & Kaufman, 2009)
5.	Minocycline	Minocin®.	Upregulation of the TrkB/BDNF pathway which promotes neurogenesis	Antibiotic	(Motaghinejad, Farokhi, Motevalian, & Safari, 2020)
6.	Celecoxib	Celebrex®.	Alleviates the levels of IL-6.	COX-2inhibitor	(M. I. Husain *et al.*, 2020)
7.	Statins	Altoprev˙	Reduce hippocampal neuroinflammation	Lowers Cholesterol	(You, Lu, Zhao, Hu, & Zhang, 2013)
8.	N-acetyl cysteine	Acetadote˙	Oxidative homeostasis, Neuroprotection	Mucolytic	(T. Palomares*et al.*, 2018)
9.	Etanercept	Enbrel˙	Reduce neuroinflammation	TNF-a receptors inhibitor	(Bayramgürler, Karson, Özer, & Utkan, 2013)
10.	Telmisartan	Micardis˙	Reduce neuroinflammation	Cardiovascular drug (angiotensin receptor blockers)	(J. Li *et al.*, 2018)

Table 2: Repurposed and conventional Pharmacological actions of miscellaneous drugs.

Sr. No	Drug	Brand name	Repurposed use	Conventional use	Reference
1.	Atomoxetine	Strattera®	Attention deficit hyperactivity disorder.	Anti-Depressant	(Garnock-Jones, & Keating, 2009)
2.	Bupropion	Wellbutrin SR®	Smoking Cessation	Anti-Depressant	(Wilkes 2008)
3.	Sildenafil	Aronix®	Erectile dysfunction	Angina	(Goldstein, Burnett, Rosen, Park, &Stecher,2019)
4.	Amphotericin B	AmBisome®	Leishmaniasis	Fungal infection	(M. Balasegaram*et al.*, 2012)
5.	Amantadine	Symmetrel®	Parkinson's Disease	Influenza	(Rascol, Fabbri, &Poewe,2021)
6.	Minoxidil	Rogaine®	Baldness	Angina	(Randolph, &Tosti2021)
7.	Bromocriptine	Cycloset®	Diabetes Mellitus	Parkinson's Disease	(Kerr, Timpe, &Petkewicz,2010)
8.	Tamoxifen	Nolvadex®	Parkinson's Disease	Inflammatory disease, Breast Cancer	(C. T. Hong*et al.*, 2017)

9.	Aspirin	Aspro Clear®	Myocardial infarction	NSAIDS	(Hurlen, Abdelnoor, Smith, Erikssen, &Arnesen, 2002)
10.	Thalidomide	Contergan®	Leprosy	Morning Sickness	(S.K. Teo *et al.*, 2002)
11.	Orlistat	Xenical®	Cancer	Obesity	(A. Czumaj *et al.*, 2019)

5. Drug Repurposing: Asset or Liability

The process of drug development is both time-consuming and expensive. It may take anywhere from 13 to 15 years and cost anywhere from 2 to 3 billion USD to bring a novel drug to market (C. Fabbriet al., 2021). The number of authorized pharmaceuticals has either stayed the same or has even reduced throughout the last few years (C. Krauset al., 2019), although the costs are on the rise. In addition, the requirements in the therapeutic domains are expanding, and the old methods of drug development are unable to meet these requirements (Ebada 2017). Regarding psychiatric drugs, it is important to emphasize that this discipline has not grown nearly as much as it should have throughout the course of time (Zhao, & So, 2018). It costs an average of USD 300 million and takes around 6.5 years to bring a new pharmaceutical to market (Ko2020). Drug repurposing is a cost-effective method that also minimizes the amount of time it takes to bring a new medication to market. In drug repurposing, it is possible to bypass the preclinical studies (Ko 2020) as well as the phase I and phase II clinical trials if these procedures have previously been completed for other purposes and the medicine's safety has been verified. As was indicated up top, the process of repurposing drugs might potentially cut down on the amount of time and money required. In addition, if the formulation can be used for the new indication without any changes, then there is no need for further formulation development. This is yet another opportunity to advance toward the goals that have been outlined. The decreased likelihood of failure owing to the medicine's already-approved adequate safety is another significant advantage of drug repurposing. Finally, the process of repurposing drugs may lead to the discovery of previously unknown illness treatment targets or pathways, which then presents additional opportunities. Although toxicity and safety are not roadblocks in the process of repurposing drugs, other challenges might cause the process to fail. These include patent considerations, regulatory concerns, and organizational difficulties. In a nutshell, many of the repurposed applications have already been stated in the past scientific literature or clinical data, which leads to restrictions in patent protection for repurposed purposes. Profitability also suffers when an existing generic formulation is modified for use in a new indication. This practice is known as "repurposing." This decrease is the result of the drug being used for purposes not specifically approved by the manufacturer. To preserve the public's interest, governments often establish guidelines on how to work together on patents that are getting close to expiring. The creation of a new formulation or dosage form, the development of new compounds with the same therapeutic effects, or the presentation of medicine in a market that is located in a different geographical location are all examples of potential techniques for turning a profit off of repurposed medications. The fact that the impact of the drug is proportional to the amount taken is yet another drawback. For this reason, it is essential to determine the optimum dosage for new indications for clinical studies (Ko 2020). Attempts to repurpose pharmaceuticals that have previously been rejected throughout the drug development process may face a further challenge in the form of investments. This problem arises as a result of the hesitation of investors, who see the failure of the treatment. Furthermore, drugs that were unsuccessful in later phases of the drug development process have less time before their patents expire to be repurposed and tried again. There is a potential reduction in the probability of failure if parallel development approaches are designed for a variety of indications.

Conclusion

To improve a patient's quality of life when they are suffering from a serious mental condition like MDD, prompt screening and treatment are required. Among the possible treatments recommended for this condition are psychotherapy, medication, and somatic therapies. Off-label usage refers to when a pharmaceutical is used in a manner that is not permitted by the manufacturer of the drug. Patients often have unsatisfactory responses to approved drugs, hence doctors often prescribe medications for unapproved uses. As a result, there was a significant need for a drug repositioning approach for the drugs used in the therapy of MDD. Drug repositioning is a process that reduces the amount of time necessary to bring medication to the market while also reducing the associated costs. In addition, since there are data available on the safety profile of the pharmaceuticals, the

chance of failure is greatly reduced, and this strategy is possible to identify new targets for the treatment of a condition. For the sake of repurposing, research has been conducted on a wide variety of pharmacological classes, such as neurotransmitter antagonists, atypical antipsychotics, and central nervous system stimulants. Nevertheless, to make this method more effective, appropriate research on the formulation, regulation, and usefulness of the medicine is necessary.

Future Perspectives

There has been a significant rise in the level of data digitalization in the healthcare sector throughout the past few years. Drug repurposing also works around the diverse data of different drug moieties, which are either in the clinical or pre-clinical phase. Nevertheless, this digitalization comes with the difficulty of gathering, analyzing, and utilizing that information to find solutions to difficult clinical situations. The ability of artificial intelligence (AI) to manage massive amounts of data while also enhancing automation is what drives the need for its use. AI is a technology-based system that can replicate human intellect by using a variety of sophisticated tools and networks. On the other hand, it does not provide a danger that might substitute the actual presence of humans. Artificial intelligence makes use of computer programs and systems that can analyze the data they are given and learn from it so that they may make choices on their own to achieve certain goals. Its applications might be employed in the pharmaceutical industry's drug discovery sector to achieve certain aims and objectives in the sector that is linked to pharmaceuticals.

Acknowledgments

Author Contribution

Conceived and designed the experiments: Amarjot Kaur Analyzed the data: Amarjot Kaur. Wrote the manuscript: Mimansa Kandhwal and Heena Khan. Visualization: Amarjot Kaur Editing of the Manuscript: Varinder Singh and Heena Khan Critically reviewed the article: Amarjot Kaur Supervision: Varinder Singh and Thakur Gurjeet Singh.

Funding

Conflict of Interest

There is no conflict of interest.

Declarations

It is an original data and has neither been sent elsewhere nor published anywhere.

References

Abbruzzese, C., Matteoni, S., Persico, M., Villani, V., & Paggi, M. G. (2020). Repurposing chlorpromazine in the treatment of glioblastoma multiforme: analysis of literature and forthcoming steps. *Journal of Experimental & Clinical Cancer Research*, *39*, 1-3. https://doi.org/10.1186/s13046-020-1534-z

Baker, N. C., Ekins, S., Williams, A. J.,& Tropsha, A. (2018). A bibliometric review of drug repurposing. *Drug Discovery Today*, *23*(3), 661-672. https://doi.org/10.1016/j.drudis.2018.01.018

Balasegaram, M., Ritmeijer, K., Lima, M. A., Burza, S., Ortiz Genovese, G., Milani, B., ... & Chappuis, F. (2012). Liposomal amphotericin B as a treatment for human leishmaniasis. *Expert opinion on emerging drugs*, *17*(4), 493-510. https://doi.org/10.1517/14728214.2012.748036

Barden, N. (2004). Implication of the hypothalamic–pituitary–adrenal axis in the physiopathology of depression. *Journal of Psychiatry and Neuroscience*, *29*(3), 185-193.

Bayramgürler, D., Karson, A., Özer, C., & Utkan, T. (2013). Effects of long-term etanercept treatment on anxiety- and depression-like neurobehaviors in rats. *Physiology & Behavior*, *119*, 145-148. https://doi.org/10.1016/j.physbeh.2013.06.010

Brent, D., Emslie, G., Clarke, G., Wagner, K. D., Asarnow, J. R., Keller, M., ... & Zelazny, J. (2008). Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. *Jama*, *299*(8), 901-913. https://doi.org/10.1001/jama.299.8.901

Brunoni, A. R., Lopes, M. &F regni, F. (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *The International Journal of Neuropsychopharmacology*, *11*(8), 1169-1180. https://doi.org/10.1017/S1461145708009309

Bryan, J. (2011). How minoxidil was transformed from an antihypertensive to hair-loss drug. *Pharmaceutical Journal*, *287*(7663), 137. https://doi.org/10.1211/PJ.2021.1.69888

Cain, R. A., (2007). Navigating the sequenced treatment alternatives to relieve depression (STAR∗ D) study: practical outcomes and implications for depression

treatment in primary care. *Primary care: Clinics in Office Practice*, *34*(3):505-519. https://doi.org/10.1016/j.pop.2007.05.006

Cha, Y., Erez, T., Reynolds, I. J., Kumar, D., Ross, J., Koytiger, G., … & Laifenfeld, D. (2018). Drug repurposing from the perspective of pharmaceutical companies. *British Journal of Pharmacology*,*175*(2), 168-180. https://doi.org/10.1111/bph.13798

Coppen, A., Shaw, D., Herzberg, B. &Maggs, R. (1967). Tryptophan in the treatment of depression. *The Lancet*, *290*(7527), 1178-1180. https://doi.org/10.1016/S0140-6736(67)91894-6

Cowen, P. J., Parry-Billings, M. &Newsholme, E. A. (1989). Decreased plasma tryptophan levels in major depression. *Journal of Affective Disorders*, *16*(1), 27-31. https://doi.org/10.1016/0165-0327(89)90051-7

Cuijpers, P., Reynolds III, C. F., Donker, T., Li, J., Andersson, G., & Beekman, A. (2012). Personalized treatment of adult depression: medication, psychotherapy, or both? A systematic review. *Depression and Anxiety*, *29*(10), 855-864. https://doi.org/10.1002/da.21985

Czumaj, A., Zabielska, J., Pakiet, A., Mika, A., Rostkowska, O., Makarewicz, W., … &Stelmanska, E. (2019). In vivo effectiveness of orlistat in the suppression of human colorectal cancer cell proliferation. *Anticancer Research*, *39*(7), 3815-3822. https://doi.org/10.21873/anticanres.13531

Delgado, P. L. (2000). Depression: the case for a monoamine deficiency. *Journal of Clinical Psychiatry*, *61*(6), 7-11.

Dell'Osso, L., Carmassi, C., Mucci, F. &Marazziti, D. (2016). Depression, serotonin and tryptophan. *Current Pharmaceutical Design*, *22*(8), 949-954. https://doi.org/10.2174/1381612822666151214104826

Dowrick, C. (2009). *Beyond depression: a new approach to understanding and management*. Oxford University Press, USA.

E Martin, A., A Schober, D., Nikolayev, A., V Tolstikov, V., H Anderson, W., E Higgs, R., … & M Witkin, J. (2017). Further evaluation of mechanisms associated with the antidepressantlike signature of scopolamine in mice. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *16*(4), 492-500.

Ebada, M. E. (2017). Drug repurposing may generate novel approaches to treating depression. *Journal of Pharmacy and Pharmacology*, *69*(11), 1428-1436. https://doi.org/10.1111/jphp.12815

Fabbri, C., Kasper, S., Zohar, J., Souery, D., Montgomery, S., Albani, D., … &Serretti, A. (2021). Drug repositioning for treatment-resistant depression: hypotheses from a pharmacogenomic study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *104*, 110050. https://doi.org/10.1016/j.pnpbp.2020.110050

Freitas, A. E., Neis, V. B., & Rodrigues, A. L. S. (2016). Agmatine, a potential novel therapeutic strategy for depression. *European Neuropsychopharmacology*, *26*(12), 1885-1899. https://doi.org/10.1016/j.euroneuro.2016.10.013

Gahr, M. (2014). Agomelatine in the treatment of major depressive disorder: an assessment of benefits and risks. *Current Neuropharmacology*,*12*(5), 387-398. https://doi.org/10.2174/1570159X12999140619122914

Garnock-Jones, K. P., & Keating, G. M. (2009). Atomoxetine: a review of its use in attention-deficit hyperactivity disorder in children and adolescents. *Pediatric Drugs*, *11*, 203-226. https://doi.org/10.2165/00148581-200911030-00005

Goldberg, J. S., Bell Jr, C. E. & Pollard, D. A. (2014). Revisiting the monoamine hypothesis of depression: a new perspective. *Perspectives in Medicinal Chemistry*, *6*, PMC-S11375. https://doi.org/10.4137/PMC.S11375

Goldstein, I., Burnett, A. L., Rosen, R. C., Park, P. W., &Stecher, V. J. (2019). The serendipitous story of sildenafil: an unexpected oral therapy for erectile dysfunction. *Sexual Medicine Reviews*, *7*(1), 115-128. https://doi.org/10.1016/j.sxmr.2018.06.005

Gurpur, P. B., Liu, J., Burkin, D. J., & Kaufman, S. J. (2009). Valproic acid activates the PI3K/Akt/mTOR pathway in muscle and ameliorates pathology in a mouse model of Duchenne muscular dystrophy. *The American Journal of Pathology*, *174*(3), 999-1008.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23(1), 56. https://doi.org/10.1136/jnnp.23.1.56

Henriksen, K., Christiansen, C., & Karsdal, M. A. (2011). Serological biochemical markers of surrogate efficacy and safety as a novel approach to drug repositioning. *Drug Discovery Today*, *16*(21-22), 967-975. https://doi.org/10.1016/j.drudis.2011.06.010

Herbert, J. (2013). Cortisol and depression: three questions for psychiatry. *Psychological Medicine*, *43*(3), 449-469. https://doi.org/10.1017/S0033291712000955

Hillhouse, T. M. & Porter, J. H. (2015). A brief history of the development of antidepressant drugs: from monoamines to glutamate. *Experimental and Clinical Psychopharmacology*, *23*(1), 1. https://doi.org/10.1037/a0038550

Holsboer, F. (2001). Stress, hypercortisolism and corticosteroid receptors in depression: implicatons for therapy. *Journal of Affective Disorder*, 62(1-2), 77-91. https://doi.org/10.1016/S0165-0327(00)00352-9

Hong, C. T., Chan, L., Hu, C. J., Lin, C. M., Hsu, C. Y., & Lin, M. C. (2017). Tamoxifen and the risk of Parkinson's disease in female patients with breast cancer in asian people: a nationwide population-based study. *Journal of Breast Cancer*, *20*(4), 356-360. https://doi.org/10.4048/jbc.2017.20.4.356

Howland, R. H. (2013).Mifepristone as a therapeutic agent in psychiatry. *Journal of Psychological Nursing and Mental Health Services*, *51*(6), 11-14. https://doi.org/10.3928/02793695-20130513-01

Hughes, J. P., Rees, S., Kalindjian, S. B., & Philpott, K. L. (2011). Principles of early drug discovery. *British Journal of Pharmacology*, *162*(6), 1239-1249. https://doi.org/10.1111/j.1476-5381.2010.01127.x

Hurlen, M., Abdelnoor, M., Smith, P., Erikssen, J., &Arnesen, H. (2002). Warfarin, aspirin, or both after myocardial infarction. *New England Journal of Medicine*, *347*(13), 969-974. https://doi.org/10.1056/NEJMoa020496

Husain, M. I., Chaudhry, I. B., Khoso, A. B., Husain, M. O., Hodsoll, J., Ansari, M. A., ... & Young, A. H. (2020). Minocycline and celecoxib as adjunctive treatments for bipolar depression: a multicentre, factorial design randomised controlled trial. *The Lancet Psychiatry*, *7*(6), 515-527. https://doi.org/10.1016/S2215-0366(20)30138-3

Institute of Health Metrics and Evaluation, 2023. Global Health Data Exchange (GHDx).

Keller, M., Montgomery, S., Ball, W., Morrison, M., Snavely, D., Liu, G., … &Reines, S. (2006). Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biological Psychiatry*, *59*(3), 216-223. https://doi.org/10.1016/j.biopsych.2005.07.013

Kerr, J. L., Timpe, E. M., & Petkewicz, K. A. (2010). Bromocriptine mesylate for glycemic management in type 2 diabetes mellitus. *Annals of pharmacotherapy*, *44*(11), 1777-1785. https://doi.org/10.1345/aph.1P271

Khan, H., Bangar, A., Grewal, A. K., Bansal, P. & Singh, T. G. (2022). Caspase-mediated regulation of the distinct signaling pathways and mechanisms in neuronal survival. *International Immunopharmacology*, *110*, 108951. https://doi.org/10.1016/j.intimp.2022.108951

Kinlein, S. A., Wilson, C. D., & Karatsoreos, I. N. (2015). Dysregulated ypothalamic–pituitary–adrenal axis function contributes to altered endocrine and neurobehavioral responses to acute stress. *Frontiers in psychiatry*, 6, 31. https://doi.org/10.3389/fpsyt.2015.00031

Ko, Y. (2020). Computational drug repositioning: current progress and challenges. *Applied Sciences*, *10*(15), 5076. https://doi.org/10.3390/app10155076

Kraus, C., Wasserman, D., Henter, I. D., Acevedo-Diaz, E., Kadriu, B., & Zarate Jr, C. A. (2019). The influence of ketamine on drug discovery in depression. *Drug Discovery Today*, *24*(10), 2033-2043. https://doi.org/10.1016/j.drudis.2019.07.007

Kupfer, D. J. (2005). The increasing medical burden in bipolar disorder. *Jama*, *293*(20), 2528-2530.10.1001/jama.293.20.2528

Law, G. L., Tisoncik-Go, J., Korth, M. J. &Katze, M. G. (2013). Drug repurposing: a better approach for infectious disease drug discovery?. *Current Opinion in Immunology*, *25*(5), 588-592. https://doi.org/10.1016/j.coi.2013.08.004

Li, J., Yang, R., Xia, K., Wang, T., Nie, B., Gao, K., ... & Wang, W. (2018). Effects of stress on behavior and resting-state fMRI in rats and evaluation of Telmisartan therapy in a stress-induced depression model. *BMC Psychiatry*, *18*(1), 1-13. https://doi.org/10.1186/s12888-018-1880-y

Little A. (2009). Treatment-resistant depression. *American family physician*, *80*(2),167-172.

Mann, J. J. (2005). The medical management of depression. *New England Journal of Medicine*, *353*(17), 1819-1834. https://doi.org/10.1056/NEJMra050730

Martinowich, K., Manji, H. & Lu, B. (2007). New insights into BDNF function in depression and anxiety. *Nature Neuroscience*, *10*(9), 1089-1093. https://doi.org/10.1038/nn1971

McGirr, A., Vöhringer, P. A., Ghaemi, S. N., Lam, R. W., & Yatham, L. N. (2016). Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. *The Lancet Psychiatry*, *3*(12), 1138-1146. https://doi.org/10.1016/S2215-0366(16)30264-4

Meyer, J. H., Ginovart, N., Boovariwala, A., Sagrati, S., Hussey, D., Garcia, A., … & Houle, S. (2006). Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. *Archives of General Psychiatry*, *63*(11),1209-1216. https://doi.org/10.1001/archpsyc.63.11.1209

Motaghinejad, M., Farokhi, N., Motevalian, M., & Safari, S. (2020). Molecular, histological and behavioral evidences for neuroprotective effects of minocycline against nicotine-induced neurodegeneration and cognition impairment: Possible role of CREB-BDNF signaling pathway. *Behavioural Brain Research*, *386*, 112597. https://doi.org/10.2174/1871527316666170309142646

Moussaieff, A., Gross, M., Nesher, E., Tikhonov, T., Yadid, G., & Pinhasov, A. (2012). Incensole acetate reduces depressive-like behavior and modulates hippocampal BDNF and CRF expression of submissive animals. *Journal of psychopharmacology*, *26*(12), 1584-1593. https://doi.org/10.1177/0269881112458729

Neumeister, A. (2003). Tryptophan depletion, serotonin, and depression: where do we stand?. *Psychopharmacology bulletin*, *37*(4), 99-115.

Nosengo, N. (2016). New tricks for old drugs. *Nature*, *534*(7607), 314-316. https://doi.org/10.1038/534314a

Nygaard, H. B., van Dyck, C. H., & Strittmatter, S. M. (2014). Fyn kinase inhibition as a novel therapy for Alzheimer's disease. *Alzheimer's research & therapy*, *6*, 1-8. https://doi.org/10.1186/alzrt238

Osterloh, I. H. (2004). The discovery and development of Viagra®(sildenafil citrate). In *Sildenafil* (pp. 1-13). Basel: Birkhäuser Basel. https://doi.org/10.1007/978-3-0348-7945-3_1

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., ... & Schatzberg, A. F. (2016). Major depressive disorder. *Nature Reviews Disease Primers*, *2*(1), 1-20. https://doi.org/10.1038/nrdp.2016.65

Palomares, T., Cordero, M., Bruzos-Cidon, C., Torrecilla, M., Ugedo, L., & Alonso-Varona, A. (2018). The neuroprotective effect of conditioned medium from human adipose-derived mesenchymal stem cells is impaired by N-acetyl cysteine supplementation. *Molecular Neurobiology*, *55*, 13-25. https://doi.org/10.1007/s12035-017-0714-0

Palumbo, A., Facon, T., Sonneveld, P., Blade, J., Offidani, M., Gay, F.,… &Harousseau, J. L. (2008). Thalidomide for treatment of multiple myeloma: 10 years later. *Blood, The Journal of the American Society of* Hematology,*111*(8), 3968-3977. https://doi.org/10.1182/blood-2007-10-117457

Pariante, C. M. (2017). Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. *European Neuropsychopharmacology*, 27(6), 554-559. https://doi.org/10.1016/j.euroneuro.2017.04.001

Plotsky, P. M., Owens, M. J., & Nemeroff, C. B. (1998). Psychoneuroendocrinology of depression: hypothalamic-pituitary-adrenal axis. *Psychiatric Clinics of North America*, *21*(2), 293-307. https://doi.org/10.1016/s0193-953x(05)70006-x

Potter, D. E., & Choudhury, M. (2014). Ketamine: repurposing and redefining a multifaceted drug. *Drug Discovery Today*, *19*(12), 1848-1854. https://doi.org/10.1016/j.drudis.2014.08.017

Prabhakar, N. K., Khan, H., Grewal, A. K. & Singh, T. G. (2022). Intervention of neuroinflammation in the traumatic brain injury trajectory: In vivo and clinical approaches. *International Immunopharmacology*, *108*, 108902. https://doi.org/10.1016/j.intimp.2022.108902

Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., … & Pirmohamed, M. (2019). Drug repurposing: progress, challenges and recommendations. *Nature Reviews Drug Discovery*,*18*(1), 41-58. https://doi.org/10.1038/nrd.2018.168

Pytka, K., Młyniec, K., Podkowa, K., Podkowa, A., Jakubczyk, M., Żmudzka, E., … &Filipek, B. (2017). The role of melatonin, neurokinin, neurotrophic tyrosine kinase and glucocorticoid receptors in antidepressant-like effect. *Pharmacological Reports*, *69*(3), 546-554. https://doi.org/10.1016/j.pharep.2017.01.026

Randolph, M., &Tosti, A. (2021). Oral minoxidil treatment for hair loss: A review of efficacy and safety. *Journal of the American Academy of Dermatology*, *84*(3), 737-746. https://doi.org/10.1016/j.jaad.2020.06.1009

Rascol, O., Fabbri, M., &Poewe, W. (2021). Amantadine in the treatment of Parkinson's disease and other movement disorders. *The Lancet Neurology*, *20*(12), 1048-1056. https://doi.org/10.1016/S1474-4422(21)00249-0

Rihal, V., Kaur, A., Singh, T. G. & Abdel-Daim, M. M. (2022). Therapeutic and mechanistic intervention of vitamin D in neuropsychiatric disorders. *Psychiatry Research*, 114782. https://doi.org/10.1016/j.psychres.2022.114782

Rodriguez, J. M., Monsalves-Alvarez, M., Henriquez, S., Llanos, M. N., & Troncoso, R. (2016). Glucocorticoid resistance in chronic diseases. *Steroids*, *115,* 182-192. https://doi.org/10.1016/j.steroids.2016.09.010

Rothstein, J. D., Patel, S., Regan, M. R., Haenggeli, C., Huang, Y. H., Bergles, D. E., ... & Fisher, P. B. (2005). β-Lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature*, *433*(7021), 73-77. https://doi.org/10.1038/nature03180

Schildkraut, J. J. (1965).The catecholamine hypothesis of affective disorders: a review of supporting evidence. *American Journal of Psychiatry*, 122(5), 509-522. https://doi.org/10.1176/ajp.122.5.509

Souery, D., Papakostas, G. I., & Trivedi, M. H. (2006). Treatment-resistant depression. *Journal of Clinical Psychiatry*, *67*, 16.

Taylor, C., Fricker, A. D., Devi, L. A., & Gomes, I. (2005). Mechanisms of action of antidepressants: from neurotransmitter systems to signaling pathways. *Cellular Signaling*, 17(5), 549-557. https://doi.org/10.1016/j.cellsig.2004.12.007

Teo, S. K., Resztak, K. E., Scheffler, M. A., Kook, K. A., Zeldis, J. B., Stirling, D. I., & Thomas, S. D. (2002). Thalidomide in the treatment of leprosy. *Microbes and Infection*, *4*(11), 1193-1202. https://doi.org/10.1016/s1286-4579(02)01645-3

Tripathy, S., Dassarma, B., Roy, S., Chabalala, H.,&Matsabisa, M. G. (2020). A review on possible modes of action of chloroquine/hydroxychloroquine: repurposing against SAR-CoV-2 (COVID-19) pandemic. *International Journal of Antimicrobial Agents*, *56*(2), 106028. https://doi.org/10.1016/j.ijantimicag.2020.106028

Tsao, C. W., Lin, Y. S., Chen, C. C., Bai, C. H. & Wu, S. R. (2006). Cytokines and serotonin transporter in patients with major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *30*(5), 899-905. https://doi.org/10.1016/j.pnpbp.2006.01.029

Weilburg, J. B. (2004). An overview of SSRI and SNRI therapies for depression. *Managed Care (Langhorne, Pa.)*, *13*(6 Suppl Depression), 25-33.

Wilkes, S. (2008). The use of bupropion SR in cigarette smoking cessation. *International Journal of Chronic Obstructive Pulmonary Disease*, *3*(1), 45-53. https://doi.org/10.2147/copd.s1121

Yang, T., Nie, Z., Shu, H., Kuang, Y., Chen, X., Cheng, J., … & Liu, H. (2020). The role of BDNF on neural plasticity in depression. *Frontiers in Cellular Neuroscience*, *14*, 82. https://doi.org/10.3389/fncel.2020.00082

You, H., Lu, W., Zhao, S., Hu, Z., & Zhang, J. (2013). The relationship between statins and depression: a review of the literature. *Expert Opinion on Pharmacotherapy*, *14*(11), 1467-1476. https://doi.org/10.1517/14656566.2013.803067

Zhang, Q. Q., Li, W. S., Liu, Z., Zhang, H. L., Ba, Y. G., & Zhang, R. X. (2020). Metformin therapy and cognitive dysfunction in patients with type 2 diabetes: a meta-analysis and systematic review. *Medicine*, *99*(10). https://doi.org/10.1097/MD.0000000000019378

Zhao, K., & So, H. C. (2018). Drug repositioning for schizophrenia and depression/anxiety disorders: a machine learning approach leveraging expression data. *IEEE journal of Biomedical and Health Informatics*, *23*(3), 1304-1315. https://doi.org/10.1109/JBHI.2018.2856535

Zheng, W., Sun, W. &Simeonov, A. (2018). Drug repurposing screens and synergistic drug-combinations for infectious diseases. *British Journal of Pharmacology*, *175*(2), 181-191. https://doi.org/10.1111/bph.13895