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**\*Corresponding author:** Alessandra Moreira de Oliveira, School of Chemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, Tel: +5521981425738; E-mail: [alessandraoliveira@eq.ufrj.br](mailto:alessandraoliveira@eq.ufrj.br)

**ORCID:** <https://orcid.org/0000-0003-4203-6637>

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## Research Article

# Antidepressants Drugs and Addiction Treatment: A development view and a technological patent landscape of drugs and compositions

Alessandra Moreira de Oliveira<sup>1\*</sup>, Suzanne de Oliveira Rodrigues Schumacher<sup>1</sup> and Adelaide Maria de Souza Antunes<sup>1,2</sup>

<sup>1</sup>School of Chemistry, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

<sup>2</sup>National Institute of Industrial Property, Rio de Janeiro, Brazil

## Abstract

**Background:** According to the World Health Organization, about 76-85% of subjects in low- and middle-income countries suffer with a mental disorder. From them the most prevalent are anxiety and depression ones, with an increase in the number of cases during the COVID-19 pandemic. Antidepressants are drugs used to treat depression, but they are also used to treat subjects addicted to drugs. The development of new technologies/drugs/compositions is important for promoting access not only to drugs, but better drugs.

**The present study aims:** 1. To carry out a survey of drugs under active development used to depression and dependency treatment (at least); 2. To evaluate, through the patent landscape, the patent documents filed in the past 10 years related to this class of drugs (antidepressants) in the context of technological scenario and 3. To promote a discussion about drugs used as antidepressants and to dependency treatment (at least).

**Results:** The search provided a scenario of a small number of drugs used for depression and drug dependency under active development, the highest development phases, the main mechanisms of action and the antidepressants used as antiaddictives. The patent landscape retrieved 2067 applied documents filed over the last 10 years, showing that China leads in the number of deposits of these drugs/compositions/methods to treat depression (with 1758 applications) made by Chinese Institutes and Universities, followed by the United States (291 applications) and Japan (193 applications). The patents' search also allowed us to evaluate the documents which the claims addressed (at least) to the treatment of depression and as antiaddictive.

**Conclusion:** The analysis of under active development drugs presented those used as antidepressants and to the treatment of substances dependency in different stages of development, including the drugs in clinical studies. Indeed, the applications' analysis on antidepressants has generated information about the technologies involved, as well as allowing the evaluation of the applications that are also promising for the treatment of addiction and depression.

## Abbreviations

ADD: Antidepressant Drug; CDDI: Cortellis Drug Discovery Intelligence; IND: Investigational New Drug; MAOIS: Monoamine Oxidase Inhibitor; SSRIs: Selective Serotonin Reuptake Inhibitor; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; PNN: Patent Publication Number; TCAs: Tricyclic Antidepressant; UAD: Under Activity Development

## Introduction

According to the World Health Organization (WHO) [1,2], there is an estimate that in low- and middle-income countries, 76–85% of subjects suffer with a mental disorder, with a lack of access to pharmacological treatment. The common mental disorders, according to the International Organization, are the anxiety disorders and depressive ones, and both of them are prevalent in the population globally. Among the depressive diseases, depression commonly occurs, due to the fact that people are living more and the population is growing. During COVID-19 pandemic, depression increases face to its devastation aspects: millions of deaths all over the world, lack of social interaction and difficulty economic situation in all countries, mainly in low- and middle income ones [3]. The development of technologies/drugs/compositions for the treatment of depression (a condition that affects the global population) translates into more access to more individualized and effective treatments. This also translates into lower suicide rates and improved therapeutic options for addict subjects and greater treatment success.

Over 300 million people all over the world suffer from depression (4.4% of the population in the world). This suggests the increase of Antidepressant Drug (ADD) industry, due to the high consumption of these drugs. Not only for depression, but also, for other conditions, such as post-traumatic stress disorder, bipolar disorder, social anxiety disorder, major depressive disorder or childhood enuresis have the ADDs as pharmacological treatment [4]. These drugs include: atypical agents, monoamine oxidase inhibitor (MAOIS), Tricyclic Antidepressant (TCAs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), selective serotonin reuptake inhibitor (SSRIs) (SNRIs and SSRI are the most used among elder adults) with different side effect profile and mechanism of action [5,6].

According to the document entitled “*Abuse Principles of Drug Addiction Treatment: A Research-Based Guide*” by the National Institute on Drug Abuse, there are drugs that can be included in the treatment of addiction (besides behavioral therapies or their combination), such as 1. Acamprosate, disulfiram and naltrexone (for alcohol dependence); 2. Naltrexone, buprenorphine and methadone (for opioid addiction) and 3. Bupropion and varenicline (tobacco addiction). Moreover, an important finding in the understanding of addicted subjects is that they often suffer from depression (in general) and the ADDs and other psychoactive medications (such as mood stabilizers, antipsychotic medications and anti-anxiety agents) are crucial for treatment effectivity [7].

## The present study aims

1. To carry out a survey of the drugs under active development used to depression and dependency treatment (at least) for the treatment of addiction to different substances and 2. To evaluate, through the patent landscape<sup>1</sup>, the patent documents filed in 10 years related to this class of drugs in the context of technological scenario and to promote a discussion about drugs used as ADD and antiaddictive (at least).

## Material and methods

Drugs Analysis from Cortellis Drug Discovery Intelligence (CDDI) Database (from Clarivate Analytics): CDDI Database focuses on drug and pharma development intelligence and provides pharmacological, chemical and biological data [9]. For the strategy search, the Database CDDI was chosen to retrieve ADDs Under Active Development (UAD) for the treatment of substance dependency, i.e., alcohol, cocaine and opioide dependency. For this purpose, the terms “*depression*” (including major depression, minor depression, postpartum depression, suicidal depression and treatment resistant depression) and “*antidepressant*” (inside the group of Psychopharmacologic Drugs) were used to the topic searches conditions associated to therapeutic group respectively in Advanced Search in CDDI Database. The mentioned strategy search was followed by the application of filters to obtain the ADDs to the treatment of substance dependency. It was not defined a period of time, due to the criteria is defined by the drugs UAD period. When a drug is UAD, this means (according to CDDI Database criteria) that it has been reported over the past 12–18 months (by Conferences, Peer Reviewed Journal Articles, Citation on the Company’s Website, Mention in Annual Reports, Clinical Trials Registers and Company Press Releases) in different development status, i.e., 1. preclinical testing; 2. Investigational New Drug (IND) filed; 3. Clinical; 4. Phases 0–III; 5. Pre-registered/registered and 6. Recommended approval [10].

Patent Landscape from Derwent Innovation Database (from Clarivate Analytics): Derwent Innovation is an analytic and patent research platform which provides access to scientific literature and patents globally [11]. Inside this database platform, it was developed a strategy search to assess technological information about ADDs. The strategy search consisted of searching for terms (antidepressant) or (depression and drug) or (depression and treatment) in the title and abstract fields, followed by the use of search codes A61P002524<sup>2</sup> (International Patent Classification from the World International Property Organization) and B14-J01A1<sup>3</sup> (Manual Code from Derwent World Patents Index). The

<sup>1</sup>Patent landscape is the analysis of patent data. It can offer a technological scenario due to it can reveal scientific, business and technological trends. Moreover, it can provide data on patent validity and other informations related to the filed document [8].

<sup>2</sup>Code for antidepressants.

<sup>3</sup>Code for antidepressants.



priority period of patent applications was 2010 – 2020. Here it will be analysed: 1 The most priority countries with the major number of applications; 2. The most institutions/universities/companies with the major number of applications; 3. The applications' temporal evolution in the past ten years; 4. A discussion of filed documents about methods/compositions/drugs claimed as ADDs and antiaddictives (at least).

## Results

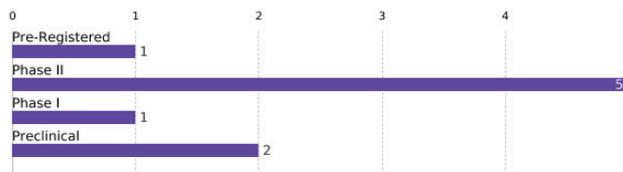
The developed strategy search, 163 drugs UAD were retrieved from Cortellis Drug Discovery Intelligence (CDDI) Database (from Clarivate Analytics). From them, 31 drugs used for substance dependency treatment, can be used to treat depression (at least). In From them: 14 drugs were used to the treatment of alcohol dependency; 12 to cocaine dependence and 2 to opioid dependency. As a drug can be used for more than one clinical condition (addiction), a total of 19 drugs used as antidepressants and alcohol, cocaine or opioid dependency were retrieved as showed in Figure 1. From the total of drugs, it was observed most of them are small molecules, which can have advantages (as ADDs), such as high potency, affinity and bioavailability [12].

Another point to highlight is about the highest phase of development of these drugs (Figure 2). Here, it is possible to observe that most of the drugs were in clinical phase (Phase I: one drug and Phase II: five drugs). Two drugs were in pre-clinical phase and only one was pre-registered. It was also highlighted that only one drug was registered.

From the developed review, a key finding emerged: the top mechanism of action of these drugs, involving molecular, cellular mechanisms and the action on receptors (Figure 3). Here, it is showed an overview of the main targets of molecule development from signal transduction modelators to specific receptors (5HT, dopanine and opioid ones).

It was also retrieved the ADDs (including) used to the treatment of substance dependency. The launched substances were excluded and only the substances UAD were showed (Table 1). Here, it is possible to identify in pre-registered phase and in clinical phase (phases I and II). The results' analysis casted a new light on about the developmenn of the drugs (ADD and Antiaddictives): 1. A few number of substance for substance treatment and depression conditions; 2. Other conditions were

### Highest Phase



**Figure 2:** The highest phases of development of the drugs (including ADDs) also used to the treatment of substance dependency. The search was carried out in September, 2021.

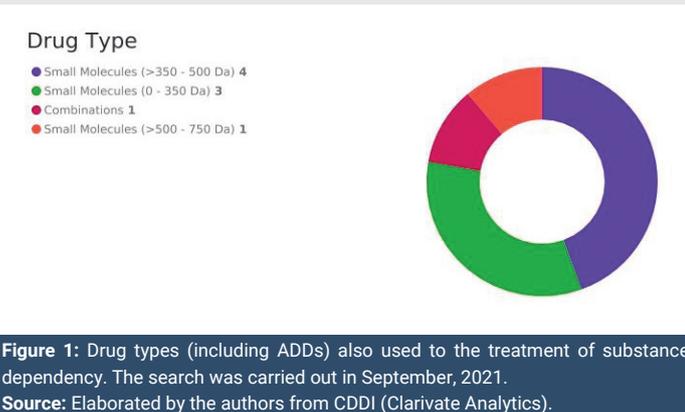
**Source:** Elaborated by the author from CDDI (Clarivate Analytics).

### Top Mechanisms of Action



**Figure 3:** Top mechanisms of action of the drugs (including ADDs) also used to the treatment of substance dependency. The search was carried out in September, 2021.

**Source:** Elaborated by the authors from CDDI (Clarivate Analytics).



**Figure 1:** Drug types (including ADDs) also used to the treatment of substance dependency. The search was carried out in September, 2021.

**Source:** Elaborated by the authors from CDDI (Clarivate Analytics).

also claimed by each substance and 3. Despite the few number of drugs, the companies (and its partnerships) are interested in the development of these therapeutic groups:

The applied search retrieved 2607 patent applied documents from Derwent Innovation Index in the period from 2010–2020. On average, 237 documents were applied per year, and in 2016 the most number of documents were applied (326). Regarding applicants (priority countries), China leads in the number of deposits (with 1758 applications) made by Chinese Institutes and Universities (as top five applicants: Henan University of Chinese Medicine (with 31 documents); Tianjin Institute of Pharmaceutical (21); Shanxi University (19); China Pharmaceutical University (17); Shanghai Institute

**Table 1:** Drugs Under Active Development (UAD) used to the treatment of dependency and depression.

Highest Phase	Code name	Generic name	Substance Treatment	Other conditions	Organization
Pre-registered	- ALKS-33-BUP - ALKS-5461	Samidorphan/ buprenorphine	Cocaine	- Antidepressants - Gastrointestinal Disorders (Not Specified)	Alkermes (Originator)
Phase II	- BTRX-246040 - LY-2940094	-	Alcohol	- Antidepressants - Antiobesity Drugs - Antiparkinsonian Drugs - Anxiolytics - Psychiatric Disorders (Not Specified)	- Lilly (Originator) - BlackThorn
Phase II	- CERC-501 - DE4G8X55F5 - JNJ-3964 - JNJ-67953964 - JNJ-67953964-AAA - LY-2456302 - LY-DMPF	Aticaprant (Rec INN; USAN)	Cocaine and Alcohol	- Antidepressants - Posttraumatic Stress Disorder - Treatment of - Psychiatric Disorders (Not Specified) - Smoking Cessation, Aid to	- Lilly (Originator) - Cerecor - Duke University - Janssen - Janssen Research & Development (Janssen) - National Institute of Mental Health
Phase II	- MAP-4343 - MePREG	- 3-Methoxyprogrenolone	Alcohol	- Antidepressants - Lesions of the Spinal Cord and Related Structures, Treatment of - Neurologic Drugs (Miscellaneous)	Mapreg (Originator)
Phase II	561679 GSK-561679 GSK-561679A NBI-77860	Verucerfont (Prop INN; USAN)	Alcohol	- Antidepressants - Congenital Malformations, Treatment of - Irritable Bowel Syndrome, Agents for - Posttraumatic Stress Disorder, Treatment of	- GlaxoSmithKline (Originator) - National Inst Alcohol Abuse Alcoholism - National Inst. Alcohol Abuse Alcoholism (National Inst Alcohol Abuse Alcoholism) - Neurocrine Biosciences
Phase II	- BPL-PSILO - COMP-360 - CYB-001 - MYCO-001 - NEO-001 - TRP-8802 - TRP-8803	Psilocybin	Cocaine and Alcohol	- Antidepressants - Alzheimer's Dementia, Treatment of - Analgesic Drugs - Antiobesity Drugs - Fibromyalgia, Treatment of - Mood Disorders, Treatment of - Neurologic Drugs (Miscellaneous) - Obsessive-Compulsive Disorder (OCD), Treatment of - Psychiatric Disorders (Not Specified) - Smoking Cessation, Aid to - Treatment of Eating Disorders - Treatment of Substance Dependency	- Beckley Psytech - COMPASS Pathways - Core One Labs - Cybin - Johns Hopkins University - Mydecine - NeonMind Biosciences - New York University - Revive Therapeutics - Sidney Kimmel Cancer Center - Tryp Therapeutics - University of Michigan - University of Wisconsin System - Usona Institute - Yale University
Phase I	- Org-34517 - PT-150 - SCH-900636	-	Alcohol	- Antidepressants - Solid Tumor Therapy	- Merck & Co. (Originator) - Organon (Merck & Co.) - Pop Test
Preclinical	- ADX-88178	-	Cocaine	- Antidepressants - Antiparkinsonian Drugs - Antipsychotic Drugs - Generalized Anxiety Disorder (GAD), Treatment of	- Addex Therapeutics (Originator) - Merck & Co.
Preclinical	-	-Divinorin A - Salvinorin A	Cocaine	- Antidepressants - Analgesic Drugs - Antidiarrheal Agents	- Harvard Medical School - Johns Hopkins University - Revixia Life Sciences

The search was carried out in September, 2021

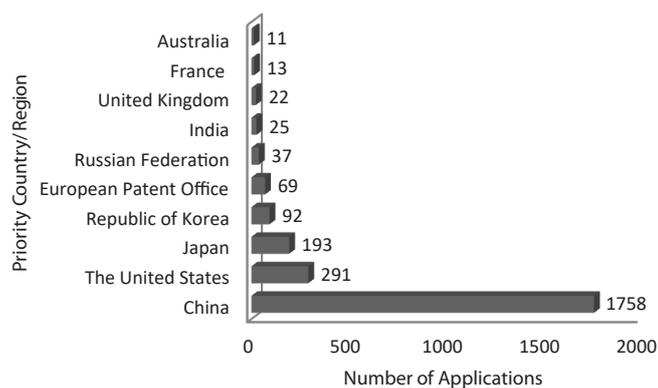
Source: Elaborated by the authors from CDDI (Clarivate Analytics)

of Pharmaceutical Industry (17) and Peking University (16). The top applicant was followed by the United States (291 applications) and Japan (193 applications) (Figures 4, 5).

Considering the use of drugs as ADD and antiaddictives (e.g), addiction disorders and depressive illness are highly prevalent [13]. Among the companies that stand out in the development of compounds to be used in pharmaceutical composition to treat depression and substance dependency (at least), there

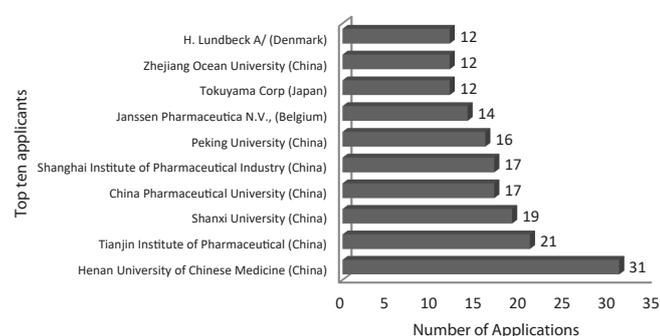
is the Japanese company TAISHO PHARMACEUTICAL CO LTD which claimed for a new carboxamide derivatives (PNN: JP2013249257A; JP2013249258A) or a new nitrogen-containing heterocyclic (PNN: WO2012036278A1).

The use of drugs to treatment can be also reported in the document applied by UMECRINE MOOD AB (from Japan). The drug can prevent central nervous system's conditions and acts as GABA-A-receptor modulator, including the



**Figure 4:** The top ten priority countries.

**Source:** Elaborated by the authors from Derwent Innovation (Clarivate Analytics). The search was carried out from 2010 -2020.



**Figure 5:** The top ten applicants.

**Source:** Elaborated by the authors from Derwent Innovation (Clarivate Analytics). The search was carried out from 2010 -2020.

activity as antidepressant, antiaddictive and antialcoholic (PPN: JP05687287B2). SUN PHARMACEUTICAL INDUSTRIES LTD. (India) applied a method to treat conditions (including depression, alcohol related disorders, addiction of narcotic agents) which are susceptible to the drug baclofen (PPN: JP2013519726A). DUKE UNIVERSITY (US) applied methods and compositions to treat psychiatric and neurologic conditions (e.g. depression, addiction) by the administration to the subject of “interfering molecule that inhibits tropomyosin-related kinase B (TrkB)-mediated activation of phospholipase C (PLC)-gamma-1” (PPN: US20110236371A1). NUTRICIA NV (Netherlands, from DANONE GROUP) applied a composition to prevent/treat disorders such as depression, abuse of alcohol/drugs, by the improvement of the fatty acid compositions of the membranes (PPN: CN104351796A).

ADD combined to cognitive behavioral can work best to depressed subjects [14]. EMORY UNIVERSITY (US) developed methods to improve behavioral therapy, by the administration of a composition with oxytocin release agent. It acts as HT1A or 5-HT2A/C or melanocortin receptor agonist to be used as antidepressant, antiaddictive, neuroleptic (e.g.) (PPN: US20120108510A1).

The use of benzodiazepine antagonist, such as flumazenil is already described in literature for benzodiazepine dependence [15,16]. Here VERITA RESEARCH PTE LTD (from Singapore)

applied a benzodiazepine antagonist in a sustained release pharmaceutical composition with a biocompatible polymer. The composition is able to form gel-like depot and can be used to the treatment of diseases by different activities: antidepressant, antiaddictive, antialcoholic, etc (PPN: AU2011279557B2). Indeed, DUQUESNE UNIVERSITY (US) claimed by the psychostimulant antidepressant/antagonist composition which is “diphenyl piperidine derivative active agent with excipient or diluent”. It can be used to treat addiction in human/animal, psychostimulant dependence and to treat depression. The application document showed that the psychostimulant dependence is amphetamine or cocaine (PPN: US20120322824A1).

Among subjects addicted to alcohol or drugs, depression is common disease. Furthermore, the substance abuse is responsible for the intensification of feelings associated with depression, such as hopelessness, sadness and loneliness [17]. The applied document by UNITED STATES DEPARTMENT OF VETERANS AFFAIRS (US) and OREGON HEALTH & SCIENCE UNIVERSITY (US) (FORMERLY OREGON HEALTH SCIENCES UNIVERSITY) claimed by a neuropsychiatric or cognitive impairment (induced by substance addiction) where it is administered in a subject a major histocompatibility complex molecule (PPN: US20120195921A1).

Finally, the development of new compounds were observed: TAKEDA PHARMACEUTICAL COMPANY LIMITED (Japan) applied a new heterocyclic compound (mechanism of action: orexin receptor antagonist) to prevent/treat diseases such as drug dependence, depression, sleep disorder and anxiety (PPN: EP3287454B1). UNIV EAST CHINA NORMAL (China) developed a new isoxazole compound to prepare drugs with antidepressant and antiaddictive activity (e.g.) (PPN: CN107459510B). A kappa opioid receptor antagonist (tetrahydroisoquinolines) to treat nicotine, alcohol, methamphetamine and cocaine addiction, depression, schizophrenia and eating disorders were claimed by RESEARCH TRIANGLE INSTITUTE (NORTH CAROLINA) (US) (PPN: JP2019531260A). Indeed, the Swiss company F. HOFFMANN-LA ROCHE applied new annellated pyridine compounds to treat disorder as drug addiction, depression, psychotic disorders, etc. (PPN: BR112012032748A2).

## Conclusion

The analysis of ADDs' technological information generated data about the treatment of depression and substance dependency, such as the development of new compounds and with different targets. Although, companies stand out (TAISHO PHARMACEUTICAL CO LTD) on drugs' research and development and a promising number of data involving ADDs were observed, there were few results also involving the treatment of addiction, which demonstrates the need for more research, development and innovation to promote more therapeutic options and more access to medicines.

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