PharmaVOICE

THERAPEUTIC DIGEST

MENTAL HEALTH REVOLUTION

IN COLLABORATION WITH thinkgen

FEBRUARY 2020

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The Mental Health Revolution

The Next Generation of Drug Development for Psychiatry

According to the National Institute of Mental Health (NIMH), nearly 46.6 million (that's one in five) U.S. adults, and almost half of adolescents (ages 13 to 18) are living with mental illnesses. This group of conditions involve changes in mood, thinking and/or behavior, and can be associated with significant distress and problems functioning in everyday activities. Mental illnesses continue to exact a heavy human and economic toll in the United States. Millions of Americans and their families are affected by mental illnesses, and the resulting lost wages, healthcare expenditures, and disability benefits account for more than $317 billion annually in the United States alone[1].

It's no surprise then that psychiatric disorders are the leading causes of disability worldwide, and there is an urgent need for new treatments. Untreated or undertreated mental illnesses have serious consequences. Life expectancy of people with severe mental illness is decreased by 13-30 years relative to the general population.

1 in 5 Americans take at least one psychiatric medication.

"Fully one in five Americans take at least one psychiatric medication. Yet when it comes to mental health, we are facing a crisis in drug innovation," says Dr. Richard Friedman, psychiatrist at Weill Cornell Medicine in a 2013 article he wrote for the *New York Times*[2]. "Even though 25% of Americans suffer from a diagnosable mental illness in any year, there are a few signs of innovation from the major drug makers." Significant hurdles to advancements came to light after a series of failed clinical trials showed novel antidepressants and antipsychotics did little to no better than placebos. "The trend was obvious at the 2011 meeting of the American Society for Clinical Pharmacology and Therapeutics, where only 13 of 300 abstracts were related to psychopharmacology and none related to novel drugs," Friedman continued.

In 2011, a report for the European College of Neuropsychopharmacology (ENCP) warned that "research in new treatments for brain disorders is under threat." With current treatments inadequate for many patients, "withdrawal of research resources is a withdrawal of hope for patients and their families," the report said. And so, for nearly a decade, advancements in the psychiatric pipeline have slowed down to a crawl.

The problem with current psychiatric drugs, according to Dr. Friedman, is that they mask two serious problems. First, each of these drug classes is filled with look-a-like drugs, which are essentially just copies of one another. Secondly, the available drugs leave a lot to be desired because patients with illnesses like schizophrenia, major depression, and bipolar disorder often fail to respond adequately to these medications or cannot tolerate their side effects.

Yet, despite their weaknesses, current therapies are effective. Furthermore, most of these drugs are now generic, meaning they are inexpensive, and many physicians have had a great deal of experience and familiarity with them.

In the past couple of years, we've seen a resurgence of development in mental health.

The seeming exodus of many pharmaceutical companies from psychiatric drug development and the lack of translation from advances in molecular mechanisms of disease and human genetics has hampered progress over the past few decades, creating a stalled revolution. But, the future looks brighter. In the past couple of years, we've seen a resurgence of development in mental health. This shift in the pipeline progress "requires challenging the conventional wisdom — upending perception, research, and drug development," says Jim Doherty, PhD, chief research officer at Sage Therapeutics. With today's technological advances, a mental health treatment golden era may finally begin.

THE CURRENT MARKET

Spending on psychotropic medications exerts considerable pressure on mental health budgets. From 1996 to 2001, the increase in real terms was 20% per year[3] with increases of 4% per year since then[4]. Switching to generics helped taper down the cost of healthcare.

However, in the mental health area, there are generic medications that are not recommended for certain medical conditions, such as epilepsy and some hormone replacement therapy, because of lack of satisfactory bioequivalence to the brand name drug[5].

Below is a chart that lists the commonly prescribed psychotropic medications by class.

Commonly Prescribed Psychotropic Medications Table 1

● *No Generics Available* ▲ *Used Off-Label*

Generic name in parenthesis

Anti-anxiety Agents	**Anti-Depressants**	**Anti-Obsessive Agents**	**Anti-Panic Agents**	**Antipsychotics** Schizophrenia & Mania	**Mood Stabilizers** Bipolar	**Stimulants** ADHD
Ativan (lorazepam)	***TRYCYCLICS***	Anafranil (clomipramine) ▲	Klonopin (clonazepam)	***TYPICAL ANTIPSYCHOTICS***	Depakene (valproic acid)	Adderall (amphetamine and dextroamphetamine)
BuSpar (buspirone)	Andafranil (clomipramine)	Luvox (fluvoxamine)	Paxil (paroxetine)	Haldol (haloperidol)	Depakote ●	Cylert (pemoline)
Centrax (prazepam)	Asendin (amoxapine)	Paxil (paroxetine)	Xanax (alprazolam)	Loxitane (loxapine)	Eskalith ●	Dexedrine (dextroamphetamine)
Inderal (propranolol) ▲	Elavil (amitriptyline)	Prozac (fluoxetine)	Zoloft (sertraline)	Mellaril (thioridazine)	Lithobid (lithium)	Ritalin (methylphenidate)
Klonopin (clonazepam) ▲	Norpramin (desipramine)	Zoloft (sertraline)	▲ *Antidepressants are also used in the treatment of panic disorder*	Moban (molindone)	Lithonate ●	▲ *Antidepressants with stimulant properties, such as Norpramin and Wellbutrin, are also used in the treatment of ADH*
Lexapro (escitalopram)	Pamelor (nortriptyline)			Navane (thiothixene)	Lithotabs ●	
Librium (chlordiazepoxide)	Sinequan (doxepin)			Prolixin (fluphenazine)	Lamactil (lamotrigine) ▲	
Serax (oxazepam)	Surmontil (trimipramine)			Serentil (mesoridazine)	Neurontin (gabapentin) ▲	
Tenormin (atenolol) ▲	Tofranil (imipramine)			Stelazine (trifluoperazine)	Tegretol (carbamazepine) ▲	
Tranxene (clorazepate)	Vivactil (protiptyline)			Thorazine (chlorpromazine)	Topomax (topiramate) ▲	
Valium (diazepam)	***SSRIs***			Trilafon (perphenazine)		
Xanax (alprazolam)	Celexa (citalopram)			***ATYPICAL ANTIPSYCHOTICS***		

▲ *Antidepressants, especially SSRIs, are also used in the treatment of anxiety*	Lexapro (escitalopram)			Abilify (aripiprazole)		
	Luvox (fluvoxamine) ▲			Clozaril (clozapine)		
	Paxil (paroxetine)			Risperdal (risperidone)		
	Paxil (paroxetine)			Seroquel (quetiapine)		
	Prozac (fluoxetine)			Zyprexa (olanzapine)		
	Zoloft (sertraline)					
	MAOIs					
	Nardil (phenelzine)					
	Parnate					
	Others					
	Desyrel (trazadone)					
	Effexor (venlafaxine)					
	Remeron (mirtazapine)					
	Serzone (nefazodone)					
	Wellbutrin (bupropion)					

Source: National Alliance on Mental Illness

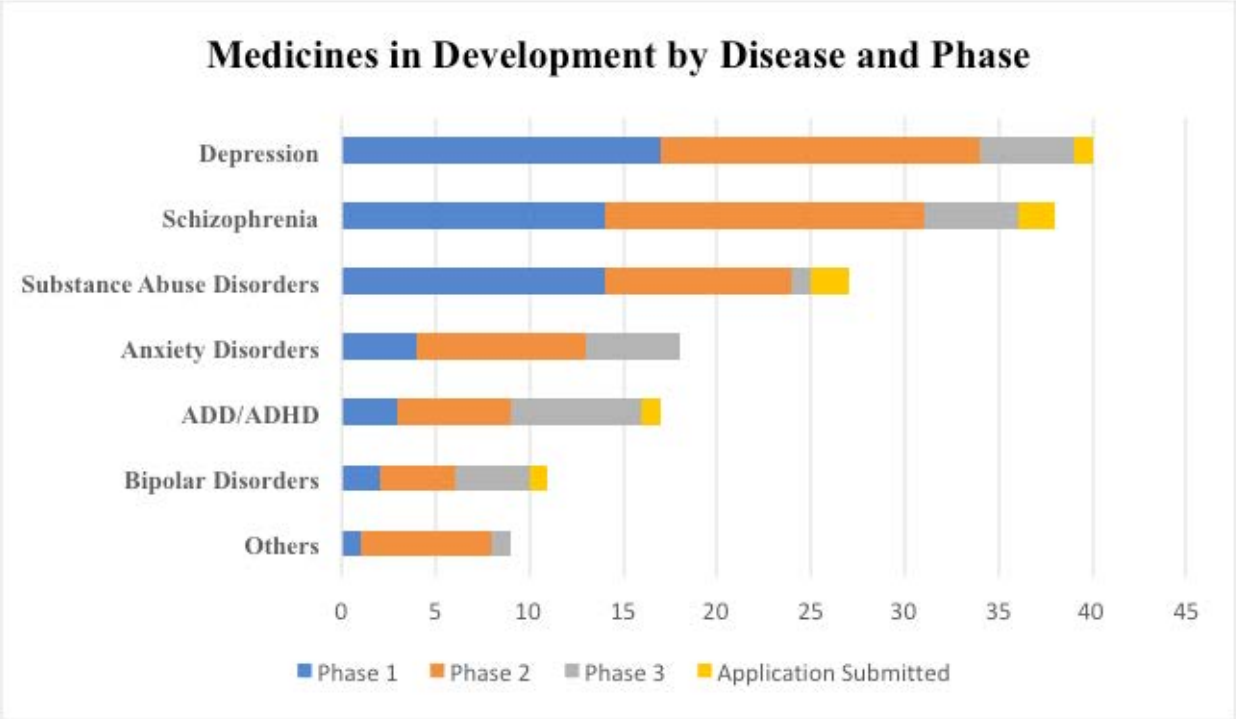
THE REVOLUTION

The development of new and effective treatments for patients with mental illness can be very challenging. The complexity of the diseases creates hurdles for researchers, with diagnoses often based on symptoms rather than underlying pathology. Recent scientific, technological, and regulatory developments coupled with collaborative efforts within the academic and pharmaceutical industries suggest that this trend may be reversing, raising hope for the community of individuals affected by mental illnesses.

The Promise of the Pipeline

Research and innovation are once again making strides in the world of mental health. This is brought on by the expanding understanding of the underlying causes of mental health diseases and can thus bring a new era in the treatment of mental illness. Current studies are examining how existing treatments work in the brain and identifying biomarkers that can be used both to improve diagnoses and assess a patient's response to therapies. Biomarkers are also being used to increasingly find new therapeutic targets through identification of the pathologies or mechanisms contributing to mental illness.

Despite the challenges that the mental health pipeline faced in the past, today there are 138 medicines in development by biopharmaceutical research companies. The promise of the pipeline is represented across a wide range of mental illnesses. This chart lists the more common psychiatric illnesses being studied.



Source: ClinicalTrials.gov

The Scientific Landscape

Novel techniques are increasingly being incorporated into the investigation of mental disorders' pathophysiology. One of the key goals is the development of personalized and precise approaches[6]. The main objective of precision medicine is to customize medical treatment to the individual characteristics of each patient.

Advances in genomic approaches to mental illnesses provide the backdrop for new opportunities.

Today, it is well established that dynamic interactions between numerous and complex pathophysiological pathways determine the expression of normal and pathological behavior. Advances in genomic approaches to mental illnesses provide the backdrop for new opportunities in drug development in psychiatry. Many of these developments are being spearheaded by the National Institute of Mental Health (NIMH), working with other institutes and centers of the National Institutes of Health (NIH).

Progress in genomics depends on collaborative efforts to acquire and study the large samples required for discovery in complex mental illnesses such as schizophrenia and major depressive disorder (MDD). The Psychiatric Genomics Consortium, a global consortium dedicated to open science and data sharing, has spearheaded the identification of hundreds of loci in the genome linked to psychiatric disorders using DNA from large cohorts (10,000–100,000)[7]. A related but independent effort the PsychENCORDE Consortium[8], has generated and shared an integrative atlas of gene expression in the human brain using samples from more than 2,000 individuals with and without mental illnesses. In short, these datasets benefit the advancement of the mental health pipeline because they reveal relationships of neuropsychiatric risk genes to biology[9], and are being mined for assumed therapeutic targets.[10]

An integrative approach is becoming increasingly necessary to several research areas in psychiatry. For example, the research in risk quantification, a process that evaluates risks that have been identified and aims to inform preventive efforts, lacks enough predictive capacity to develop robust models to detect risk thresholds. This might explain why the traditional hypothesis-driven research has produced frustrating results in the field of biomarkers.[11]

Novel techniques such as metabolomics to mental illness research is becoming one of the most prominent platforms, and the vast majority of papers in this field have only been recently published in the last five years. Metabolomics has been defined as the study of the global metabolites profile in a system (cell, tissue, or organism) under a given set of conditions[12]. These technologies allow the global analysis of one or more biological systems at a time at a molecular level versus having to study their components individually[13]. This advancement, however, presents still unanswered questions on the practical applicability of metabolomics: on how the data are collected and interpreted and about the potential limitations of metabolomics studies.[14]

Earlier hopes that gene discoveries would rapidly yield targets for drugs with novel mechanisms of action (MOA) have been largely unfulfilled[15], but the approach still has value. Targets emerging from genomic approaches can follow a linear path from identification to validation and testing with new tools available to both academia and industry. These include methods to quantify target engagement in living subjects such as positron emission tomography (PET) tracers to assess molecular interactions, as well as high-density electroencephalography and functional magnetic resonance imaging (fMRI) to measure effects of drugs on brain circuits. We can now assess whether manipulating previously untestable targets alters domains of brain function relevant to psychiatric disorders and, when coupled with clinical trials, correlate to measures of safety and efficacy.

The use of clinical metabolomics, PET, and fMRI in psychiatry essentially help identify biomarkers, which can be used as an indicator of a particular disease state. Identifying these biomarkers is a crucial step to developing more efficacious medications as we move forward in the mental health pipeline.

The Technological Landscape

The digitization of health has been exploding over the last decade.

The next era of digital health has arrived. The digitization of health has been exploding over the last decade, from its early days of Quantified Self (QS), general wellness and health monitoring, to the now much more advanced technologies that can provide evidence-based clinical interventions and disease treatments. Digital therapeutics (DTx) is a subset of digital health, a large, growing field encompassing a multitude of technologies, products and services across healthcare and wellness industries.

The promise for digital health for mental health is significant.

"I think the promise of digital health for mental health is significant. We haven't been making much progress of late in terms of our ability to treat patients. Digital health offers is the opportunity to connect with patients between visits, to bring different therapeutic modalities to patients, particularly symptom monitoring and psychotherapy, into people's home, into their lives day to day," says Dr. Carl Marci, former chief medical officer of CompanionMx, part-time psychiatrist at the department of psychiatry at Massachusetts General Hospital, and professor of psychiatry at Harvard Medical School. According to Dr. Marci, one of the problems for mental health is daily symptom monitoring. "Patients come into my office, at most two weeks, more typically every two months, and I see them for 10-15 minutes and they tell me through their biased brain and limited recall how they've been doing for the past few days or weeks. The ability to collect symptom information more frequently by self-report, but also by using a range of tools that are in smartphones, including accelerometers, or GPS or voice technologies to capture non-conscious processing that does not require a survey for monitoring symptoms in mental health is very exciting."

Digital therapeutics use digital solutions to change patient behavior and lifestyle, usually with the help of a smartphone and delivered through an app. These apps could enhance, and in some cases, replace medications for treating a range of mental disorders.[16] Apps have been successfully used to treat many chronic diseases such as Type 2 diabetes, obesity, substance abuse, ADHD, anxiety, depression, and many others. The most common application of digital therapeutics in mental health is the digital delivery of cognitive behavioral therapy (CBT), a psycho-social intervention aimed to improve mental health. However, up until recently, this space has not been supervised under the guidance of the FDA.

Prescription digital therapeutics (PDT) have entered the commercial arena as a new approach to disease management. The difference between digital therapeutics and PDT go beyond semantics. "The whole space around digital therapeutics versus prescription digital therapeutics are different," explains Kirsten Carlson, VP of marketing at Pear Therapeutics. "Digital therapeutics are health and wellness apps and they're not regulated by the FDA. PDT is the newest therapeutic class in healthcare — where biology and software technology intersect. This means we have gone through the clinical rigor under FDA guidance. It means safety and efficacy are tested in randomized clinical trials with evidence to support our claims, and a product label through FDA clearance."

PDT as a commercial therapeutic category was pioneered by Pear Therapeutics, which has developed an app called reSET. reSET delivers CBT for substance-abuse disorder. It was approved by the FDA in 2017, followed shortly by reSET-O, a PDT for opioid abuse disorders approved the year after. Pear also developed a treatment for insomnia and depression, called Somryst, which was submitted to the FDA for approval in July 2019.

Prescription digital therapeutics is a young therapeutic category.

Prescription digital therapeutics is still a young therapeutic category that has few players in the field. Pear Therapeutics has a lengthy pipeline that includes PDT for pain, PTSD, bipolar disorder, and many others. However, candidates such as Alkili's AKL-T01 studied for its effect on ADHD, and Cognoa leading the PDT path in autism are not far behind.

As PDT becomes more commonplace in the therapeutic landscape, it is important for the FDA to collaborate with the digital therapeutics companies to create systems that would regulate digital systems but also allow for improvements and upgrades. The regulations for pharmaceutical therapeutics that contain a molecule that doesn't change versus digital health that has technology that needs constant tweaking is different. "Let's say a [digital health] company has an approved indication for one of its tools. And let's say it has an update for it. Does the company have to go back through the FDA? Does it need to go back through clinical trials?" Dr Marci asks. "Those are the things that are being worked out now."

The Regulatory Landscape

These scientific opportunities are helped along by federal regulators who recognize that drug development for unmet medical needs like serious mental illness requires additional support.

In 2012, the US Food and Drug Administration (FDA) Safety and Innovation Act created the "Breakthrough Therapy" designation to expedite development of promising drugs intended to treat serious or life-threating conditions. This provides more intensive feedback and expedited review than the earlier Fast Track designation.[17] The FDA has issued guidance that reflect its current thinking on drug development tools,[18] biomarker qualification for specific contexts of use, and in psychiatry, trial designs for antidepressant drugs[20].

There is a parallel renewed interest in psychiatric therapeutics by the pharmaceutical industry. In March 2019, the FDA approved two new antidepressant medications: Janssen's Spravato (esketamine nasal spray) for treatment-resistant depression, and Sage Therapeutics' Zulresso (intravenous brexanolone) for postpartum depression. Both are mechanistically novel and act rapidly, driving clinical improvement in hours to days instead of three to four weeks for traditional antidepressants. Both received "Breakthrough Therapy" designations before approval. More generally, for all FDA new drug approvals in 2018, 24% had breakthrough therapy designations.[21]

The future of psychiatric medications is beginning to look up. Table 2 presents an overview of the psychiatric drug pipeline from 2013 to present. Nine promising drug candidates have been granted 11 breakthrough therapy designations, including brexanolone and esketamine. These include three additional rapidly acting antidepressants, as well as mechanistically new compounds for schizophrenia, autism, and post-traumatic stress disorder. Six received fast track designations for depression and schizophrenia. Many novel mechanisms are represented among the drugs in early phase testing, suggesting opportunities for truly transformative treatments.

Collaborative Approaches that Support Drug Development

Collaboration between traditional pharmaceutical therapeutics and digital health is on the rise.

As pharmaceutical companies begin to explore the true value and potential of technology, it is difficult as to ascertain to what extent these partnerships are going to drive change in the mental health pipeline. Nevertheless, collaboration between traditional pharmaceutical therapeutics and digital health is on the rise. "We see a trend of using apps in clinical trials for new pharmaceuticals," Dr. Marci says. "We're looking to apps and digital health platforms that can do a better job of symptom monitoring, or in some cases, an aid to diagnosis or add-on to the treatment. What we're seeing is more of a collaboration between the pharmaceutical industry and the app world." For example, if a big pharma company that is developing a medication indicated for bipolar disorder, and a small company with an app that allows for symptom monitoring of bipolar disorder collaborated, "then they could form a partnership where the pharmaceutical company could help underwrite the necessary clinical trials and the app developers could help improve on and get the data to improve the app, which can be prescribed as a combination package down the road," Dr. Marci continues. The challenge has shifted from identifying a complementary technology to selecting the right company with which to partner.

Various groups support both drug discovery and tools for drug development. One such consortium is the Alzheimer's Disease Neuroimaging Initiative, a public-private partnership coordinated by the NIH and the Foundation for the NIH (FNIH). This initiative follows the use of cerebrospinal fluid and PET imaging biomarkers as they are used in clinical trials to enroll patients with pathological brain changes that was only previously detected after death. The biomarker data are also being used to interpret clinical trial data[22].

Most recently, the FNIH has turned its attention to the opportunities in psychiatry, helping coordinate the Autism Biomarkers Consortium project alongside the NIMH and other partners. This project focuses on validating biomarkers to inform treatment development[23].

At the same time, the NIMH has been fostering smaller scale efforts such as the FAST-Fail initiative, which is aimed at testing mechanistic hypotheses that underlies potential treatments. One of the FAST-fail projects assessed whether κ-opioid receptor antagonism enhances activation of the reward circuitry in the human brain as measured by fMRI response to a monetary incentive delay.[24] This study was able to track biomarkers associated with anhedonia, a core symptom of depression.

The North American Prodromal Longitudinal Study (NAPLS)[25], funded by NIMH, is another organization that aims to define disease trajectory, points of intervention, and outcomes of individuals at high risk of psychosis. NAPLS works together with the Philadelphia Neurodevelopmental Cohort[26], PRONIA[27], and PSYSCAN[28] in an international consortium called Harmonization of At Risk Multisite Observational Networks for Youth (HARMONY) to develop and cross-validate biomarkers and clinical-behavioral risk predictors of disease trajectory in individuals at Clinical High Risk for psychosis. These projects are poised to inform studies of early interventions for psychotic syndromes[29].

Most recently, a consortium was started by the FNIH Accelerating Medicine Partnership on schizophrenia, helped along by the National Alliance on Mental Illness, that may be able to detect one or more developmental pathophysiologies that could be responsive to early interventions.

PSYCHIATRIC DRUG PIPELINE (2013-2019) Table 2

★*RAAD: Rapid Acting Anti-Depressants*

Early Phase 1 Phase 1 Phase 2 Phase 2/3

FDA Breakthrough Therapy Designations	MOA	Indication	Company	Date of Designation
SEP-363856	5-HT1A receptor agonist and TAAR1 receptor agonist	Schizophrenia	Sunovion Pharmaceuticals	May 2019
AXS-05 *fixed dose combination of dextromethorphan and bupropion*	NMDA receptor antagonist/ σ-1 receptor agonist and NDRI	Treatment-resistant depression	Axsome Therapeutics	March 2019
reSET-O	Cognitive Behavioral Therapy	Opioid abuse disorder	Pear Therapeutics	December 2018
NRX-101 *fixed dose combination of D-cycloserine and lurasidone*	NMDA receptor antagonist and 5-HT2A receptor antagonist	Severe bipolar depression with acute suicidal ideation and behavior (RAAD) ★	NeuroRx	November 2018
SAGE-217	GABA-A receptor positive allosteric modulator	Major depressive disorder (RAAD) ★	Sage Therapeutics	February 2018
balovaptan (RG7314, ROS285119)	V1A receptor antagonist	Autism spectrum, social communication	Hoffman-LaRoche	February 2018
pimavanserin (Nuplaxid™)	5-HT2A receptor inverse agonist, less so at 6-HT2C receptor	Dementia-related psychosis	Acadia Pharmaceuticals	October 2017
MDMA-assisted psychotherapy for post-traumatic stress disorder	Indirect serotonin agonist	Post-traumatic stress disorder	COMPASS Pathways	August 2017
brexanolone (SAGE-547)	GABA-A receptor positive allosteric modulator	Post-partum depression (RAAD) ★	Sage Therapeutics	September 2016
esketamine	Non-competitive NMDA receptor antagonist	Major depressive disorder with imminent risk of suicide (RAAD) ★	Janssen Pharmaceutical	August 2016
pimavanserin (Nuplaxid™)	5-HT2A receptor inverse agonist, less so at 5-HT2C receptor	Hallucinations and delusions in Parkinson's disease psychosis	Acadia Pharmaceuticals	April 2016

rapastinel (GLYX-13, BV102)	NMDA receptor partial agonist	Major depressive disorder, adjunctive treatment (RAAD) ★	Allergan	January 2016
aripiprazole lauroxil extended release (Aristada™)	D2 receptor and 5-HT1A receptor partial agonist, 5-HT2A receptor antagonist	Schizophrenia	Alkermes	October 2015
cariprazine (Vraylar™)	D2 receptor and 5-HT1A receptor partial agonist, 5-HT2A receptor antagonist	Schizophrenia; manic or mixed episodes associated with bipolar disorder	Allergan	September 2015
brexpiprazole (Rexulti™)	5-HT1A receptor and D2 receptor partial agonist, 5-HT2A receptor antagonist	Major depressive disorder adjunctive treatment; schizophrenia	Otsuka Pharmaceutical Company	July 2015
NaBen (SND-13)	DAAO inhibitor	Schizophrenia, adjunctive treatment	SyneuRx International	December 2014
pimavanserin	5-HT2A receptor inverse agonist, less so at 5-HT2C receptor	Hallucinations and delusions in Parkinson's disease psychosis	Acadia Pharmaceuticals	September 2014
esketamine	Noncompetitive NMDA receptor antagonist	Treatment-resistant depression (RAAD) ★	Janssen Pharmaceutical	November 2013
vortioxetine (Brintellix™)	SSRI, 5-HT3 receptor antagonist, 5-HT1A receptor agonist	Major depressive disorder	Takeda Pharmaceutical Company	October 2013
levomilnacipran (Fetzima™)	SNRI	Major depressive disorder	Forest Laboratories	July 2013
FDA Fast Track Designations	**MOA**	**Indication**	**Company**	**Date of Designation**
rapastinel	NMDA receptor partial agonist (glycine site partial agonist)	Major depressive disorder, adjunctive treatment (RAAD) ★	Naurex	March 2014
AVP-786 *fixed dose combination of*	σ-1 receptor agonist/ uncompetitive NMDA receptor antagonist/ SNRI and cytochrome P450 2D6 inhibitor	Agitation in Alzheimer's disease	Avanir Pharmaceuticals	November 2015

AXS-05 *fixed dose combination of dextromethorphan and bupropion*	NMDA antagonist and 5-HT2A receptor antagonist/ σ-1 receptor agonist and NDRI	Treatment-resistant depression	Axsome Therapeutics	February 2017
NRX-101 *fixed dose combination of D-cycloserine and lurasidone*	NMDA antagonist and 5-HT2A receptor antagonist	Severe bipolar depression with acute suicidal ideation and behavior (RAAD) ★	NeuroRx	August 2017
lumateperone (ITI-007)	5-HT2A receptor antagonist, DPPM	Schizophrenia	Intra-Cellular Therapeutics	November 2017
AV-101	NMDA receptor glycine B site antagonist	Major depressive disorder, adjunctive treatment (RAAD) ★	VistaGen Therapeutics	January 2018
AGN-241751	NMDA receptor modulator	Major depressive disorder	Allergan	January 2018
FDA New Drug Approvals	**MOA**	**Indication**	**Company**	**Date of Designation**
esketamine, intranasal (Spravato™)	Noncompetitive NMDA receptor antagonist	Treatment-resistant depression, adjunctive treatment (RAAD) ★	Janssen Pharmaceutical	March 2019
brexanolone, intravenous (Zulresso™)	GABA-A receptor positive allosteric modulator	Post-partum depression (RAAD) ★	Sage Therapeutics	March 2019
reSET	Cognitive Behavioral Therapy	Substance abuse disorder	Pear Therapeutics	December 2018
deutrabenazine (Austedo™)	VMAT2 inhibitor	Tardive dyskinesia in adults	Teva Pharmaceutical Industries	August 2017
valbenazine (Ingrezza™)	VMAT2 inhibitor	Tardive dyskinesia in adults	Neurocrine Biosciences	April 2017
New Drug Application Submissions	**MOA**	**Indication**	**Company**	**Date of Submission**
Somryst	Cognitive Behavioral Therapy	Insomnia	Pear Therapeutics	July 2019
rykindo (LY03004)	Risperidone extended-release microsphere	Schizophrenia	Luye Pharma Group	March 2019
lumateperone (ITI-007)	5-HT2A receptor antagonist, DPPM	Schizophrenia	Intra-Cellular Therapeutics	December 2018

ALKS 5461 *fixed sose combination of samidorphan and buprenorphine*	μ opioid receptor antagonist/partial agonist at μ and κ opioid receptors, antagonist at δ opioid receptor	Major depressive disorder adjunctive treatment	Alkermes	April 2018
HTL0014242 *Early Phase 1*	mGluR5 negative allosteric modulator	Neurology indications	Heptares Therapeutics	
HTL0016878 *Early Phase 1*	M4 receptor agonist	Neurobehavioral symptoms associated with Alzheimer's disease	Heptares Therapeutics	
AUT00206 *Early Phase 1*	Kv3.1/3.2 potassium channel modulator	Schizophrenia, Fragile X syndrome	Autifony Therapeutics	
Sage-718 *Early Phase 1*	NMDA receptor positive allosteric modulator	Huntington's disease	Sage Therapeutics	
AKL-T03 and AKL-T04 *Early Phase 1*	Cognitive Behavioral Therapy	Major Depressive Disorder	Akili	
CORTI118335	GR modulator, MR antagonist	Schizophrenia, adjunctive therapy for treating obesity	Corcept Therapeutics	
NV-5138 *Phase 1*	Sestrin2 modulator/ mTORC1 activator	Treatment-resistant depression, major depressive disorder (RAAD) ★	Navitor Pharmaceuticals	
AKL-T02 *Phase 1*	Cognitive Behavioral Therapy	Autism Spectrum Disorder	Akili	
CVN058 *Phase 1*	5-HT3 receptor antagonist	Cognitive improvement associated with schizophrenia, mismatch negativity biomarker study	Cerevance Alpha	
LY03005 (ansofaxine) *Phase 1*	SNDRI, prodrug of desvenlafaxine	Major depressive disorder	Luye Pharma Group	
LY03010 *Phase 1*	Paliperidone, intramuscular injection	Schizophrenia	Luye Pharma Group	
TAK-041 *Phase 1*	GPR139 agonist	Schizophrenia	Takeda Pharmaceutical Companu	

KAR-004 *fixed dose combination of xanomeline and trospium (KarXT)* *Phase 2*	M1/M4 receptor agonist and peripherally-selective pan muscarinic receptor antagonist	Schizophrenia	Karuna Therapeutics	
Lu AF11167	PDE10 inhibitor	Schizophrenia, negative symptoms	H. Lundbeck A/S	
BI 425809 plus behavioral training *Phase 2*	glyT1 inhibitor	Schizophrenia	Boehringer-Ingelheim Pharmaceuticals	
Drugs in Early Phase Clinical Trials (Currently Recruiting) *with FDA Breakthrough Therapy Designations*	**MOA**	**Indication**	**Company**	
TAK-831 *Phase 2*	DAAO Inhibitor	Schizophrenia	Takeda Pharmaceutical Company	
AKL-T01 *Phase 2*	Cognitive Behavioral Therapy	ADHD	Akili	
BI 425809 *Phase 2*	glyT1 inhibitor	Schizophrenia, add-on treatment for cognitive impairment	Boehringer-Ingelheim Pharmaceuticals	
BI 409306 *Phase 2*	PDE9 inhibitor	Schizophrenia	Boehringer-Ingelheim Pharmaceuticals	
ASP4345 *Phase 2*	D1 receptor modulator	Schizophrenia, add-on for cognitive impairment	Astellas Pharma	
basmisanil *Phase 2*	GABA-A α5 negative allosteric modulator	Cognitive impairment associated with schizophrenia	Hoffman-LaRoche	
BIIB104 (PF-04958242) *Phase 2*	AMPA receptor positive allosteric modulator	Cognitive impairment associated with schizophrenia	Biogen	
TAK-041 *Phase 2*	GPR139 agonist	Schizophrenia, motivational anhedonia (monetary incentive delay task), add-on to anti-psychotic drugs	Takeda Pharmaceutical Company	

RO6889450 *Phase 2*	Undisclosed mechanism, effects on DA synthesis capacity	Schizophrenia	Hoffman-LaRoche	
lumateperone (ITI-007) *Phase 2*	5-HT2A receptor antagonist, DPPM	Schizophrenia	Intra-Cellular Therapeutics	
esketamine *Phase 2*	NMDA receptor antagonist glycine site partial agonist	Treatment-resistant depression, treatment-resistant bipolar disorder	Janssen Pharmaceutical	
SEP-4199 *Phase 2*	Undisclosed mechanism	Major depressive disorder episodes in bipolar 1 depression	Sunovion Pharmaceuticals	
MIJ821 *Phase 2*	NMDA receptor 2B-selective negative allosteric modulator	Treatment-resistant depression	Novartis Pharmaceuticals	
pimavanserin (Nuplaxid™) *Phase 2*	5-HT2A receptor inverse agonist and antagonist, less so at HT2C receptor	Depression in Parkinson's disease	Acadia Pharmaceuticals	
SEP-363856 *Phase 2*	5-HT1A receptor agonist and TAAR1 receptor agonist	Parkinson's disease psychosis	Sunovion Pharmaceuticals	
vortioxetine *Phase 2*	SSRI, 5-HT3 receptor antagonist, 5-HT1A receptor agonist	Major depressive disorder	Takeda Pharmaceutical Company	
MIN-117 *Phase 2*	5-HT1A and 5-HT2A receptor antagonist, SDRI, alpha 1 adrenergic receptor agonist	Major depressive disorder	Minerva Neurosciences	
rapastinel (GLYX-13, BV-102) *Phase 2*	NMDA receptor partial agonist	Rapid treatment of suicidality in major depressive disorder (RAAD) ★	Allergan	
AV-101 *Phase 2*	NMDA receptor glycine B site antagonist	Major depressive disorder adjunctive treatment	VistaGen Therapeutics	
NRX-101 *fixed dose combination of D-cycloserine and lurasidone* *Phase 2*	NMDA receptor antagonist and 5-HT2A receptor antagonist	Bipolar depression, Glx (glutamate plus glutamine) biomarker study (RAAD) ★	NeuroRx	
JNJ-18038683 *Phase 2*	5-HT7 receptor antagonist	BPD, cognition and depression	Janssen Pharmaceutical	

JNJ-42165279 *Phase 2*	FAAH inhibitor	Autism spectrum disorder, Autism Behavior Inventory core domain	Janssen Pharmaceutical	
balovaptan (RO5285119) *Phase 2*	V1A receptor antagonist	Autism spectrum disorder	Hoffman-LaRoche	
SRX246 *Phase 2*	V1A receptor antagonist	Post-traumatic stress disorder	Azevan Pharmaceuticals	
Cannabis *Phase 2*	CB1 receptor agonist plus other activities	Post-traumatic stress disorder	Tilray Pharmaceutical	
troriluzole (BHV-4157) *Phase 2*	Glutamate modulator (prodrug of riluzole)	Obsessive-compulsive disorder	Biohaven Pharmaceuticals, Inc	
SXC-2023 *Phase 2*	Cystine-glutamate antiporter activator	Obsessive-compulsive disorder adjunctive treatment	Promentis Pharmaceuticals, Inc.	
NaBen SND-13 *Phase 2/3*	DAAO inhibitor	Schizophrenia, add-on treatment	SyneuRx International	
NRX-101 *fixed fose combination of D-cycloserine and lurasidone* *Phase 2/3*	NMDA receptor antagonist and 5-HT2A receptor antagonist	Schizophrenia. Glx (glutamate plus glutamine) biomarker validation study (RAAD) ★	NeuroRx	
Pear-004 *Phase 2/3*	Cognitive Behavioral Therapy	Schizophrenia	Pear Therapeutics	
AVP-786	σ-1 receptor agonist/ uncompetitive NMDA receptor antagonist/ SNRI and cytochrome P450 2D6 inhibitor	Schizophrenia	Avanir Pharmaceuticals	

Sources: ClinicalTrials.gov, FDA, and company websites

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CB1, cannabinoid 1 receptor subtype; DA, dopamine; D2, dopamine 2 receptor subtype; DAAO, D-amino acid oxidase; DPPM, dopamine receptor phosphoprotein modulator; FAAH, fatty acid amide hydrolase; GABA-A, gamma-aminobutyric acid A; GPR, G-protein coupled receptor; GR, glucocorticoid receptor; glyT1, glycine transporter 1; 5-HT, 5-hydroxytryptamine (serotonin); M1/M4, muscarinic cholinergic receptor subtypes; mGluR5, metabotropic glutamate receptor 5; MR, mineralocorticoid receptor; mTORC1, mammalian target of rapamycin complex 1; NDRI, norepinephrine and dopamine uptake inhibitor; NE, norepinephrine; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; RAAD, rapid-acting antidepressant; SDRI, serotonin and dopamine reuptake inhibitor; SNDRI, serotonin, norepinephrine, and dopamine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TAAR1, trace amine-associated receptor 1; V1A, vasopressin V1A; VMAT2, vesicular monoamine transporter 2

CONCLUSION

New and novel treatments of mental illnesses have not advanced as robustly in recent years compared with treatments for other disease categories. There have, however, been great strides in identifying biomarkers in psychiatry. “One of the challenges is that the diagnostic categories we have are not based on biology, ” Dr. Marci explains. “They are based on committees and consensus review of patients based on patient’s self-report clinical interviews. I’ve spent a long time espousing the limitations of self-reporting for the purposes of understanding people’s brains. Our conscious brain is only a small part; therefore, we need tools that can measure non-conscious processing to do a better job of formulating diagnostic categories like depression for example.”

New approaches to decipher the biological relevance of psychiatric risk genes are needed in order to translate these findings into effective pharmaceuticals. The FDA encourages novel approaches. Pharmaceutical companies remain engaged in assessing biomarkers, and academic research is identifying new disease characteristics. Thus, while frustration at recent failed research exists, the pipeline is increasingly robust and provides a promising path for novel drug applications in areas of unmet or underserved medical need.

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