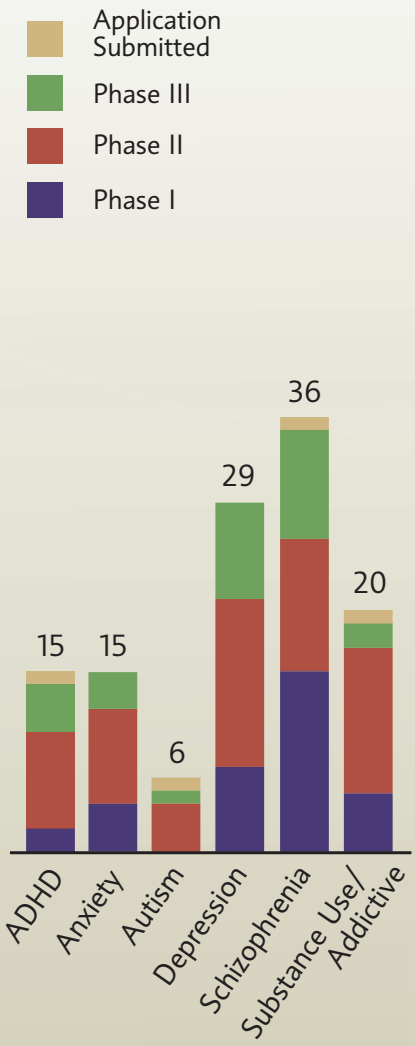
MEDICINES IN DEVELOPMENT FOR

Mental Health

PRESENTED BY AMERICA'S BIOPHARMACEUTICAL RESEARCH COMPANIES

2014 REPORT

Medicines in Development For Mental Health



Some medicines are listed in more than one category.

Biopharmaceutical Research Companies Are Developing More Than 100 Medicines to Treat Mental and Addictive Disorders

Mental health conditions exact a heavy human and economic toll in the United States. The National Institute of Mental Health (NIMH) estimates that 1 in 4 American adults—61.5 million—have been diagnosed with a mental health disorder. According to the NIMH, serious mental illnesses cost the United States more than $317 billion annually in lost wages, health care expenditures and disability benefits.

Biopharmaceutical research companies are currently **developing 119 medicines** to help people who have some type of mental disorder, such as anxiety, depression, schizophrenia, or substance use disorders. Those medicines are either in clinical trials or awaiting review by the U.S. Food and Drug Administration (FDA), with more than 75 percent of the medicines in the earliest phases of research and development—a time when potential treatments often face difficult hurdles and setbacks.

Over the past half century, biopharmaceutical research has helped alleviate the burden and improve the quality of life for many individuals living with a mental disorder. But therapeutic advances are needed for people not helped by current treatments or for those who experience negative side effects. Further research into new or improved treatments is dependent on developing a better understanding of how current treatments work, identifying biomarkers that can be used to improve diagnosis and assess responses to therapies, and finding new therapeutic targets through identification of the pathologies or mechanisms contributing to mental disorders.

Examples of some medicines now being tested to treat specific mental disorders include:

- A triple reuptake inhibitor that may provide a broader spectrum of therapeutic activity for **attention-deficit/ hyperactivity disorder (ADHD)**.

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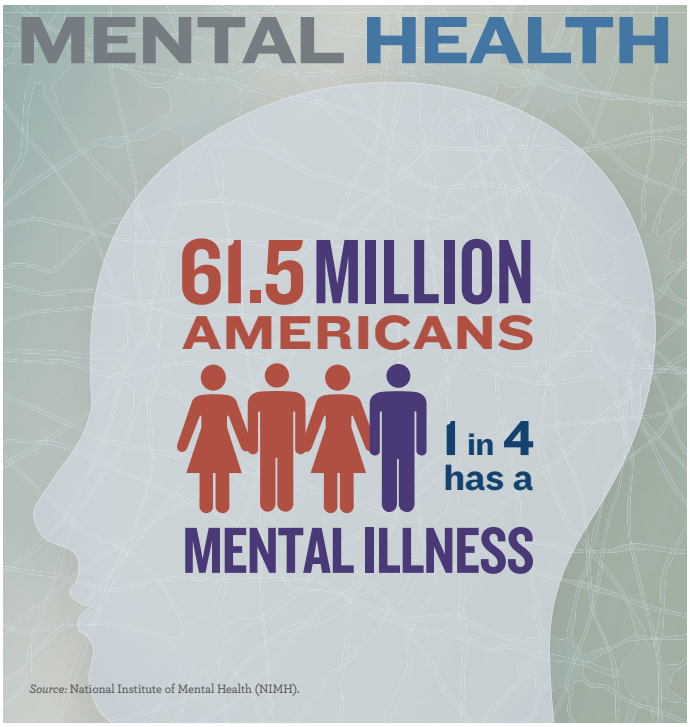
RESEARCH • PROGRESS • HOPE



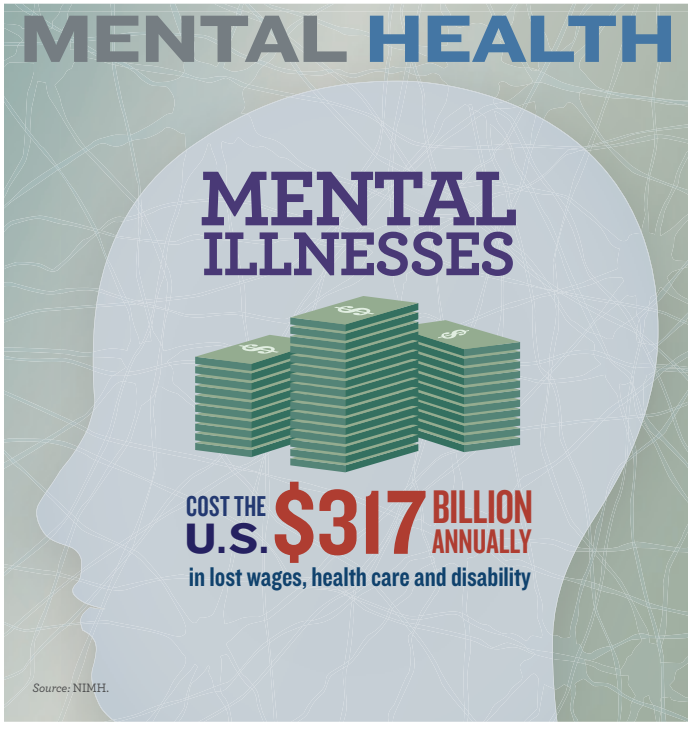
- An intranasal medicine for **treatment-resistant depression** that targets a receptor in the brain resulting in a rapid onset of antidepressant effects.
- A medicine for **schizophrenia** that targets a known treatment pathway but with potentially fewer negative side effects than existing treatments.

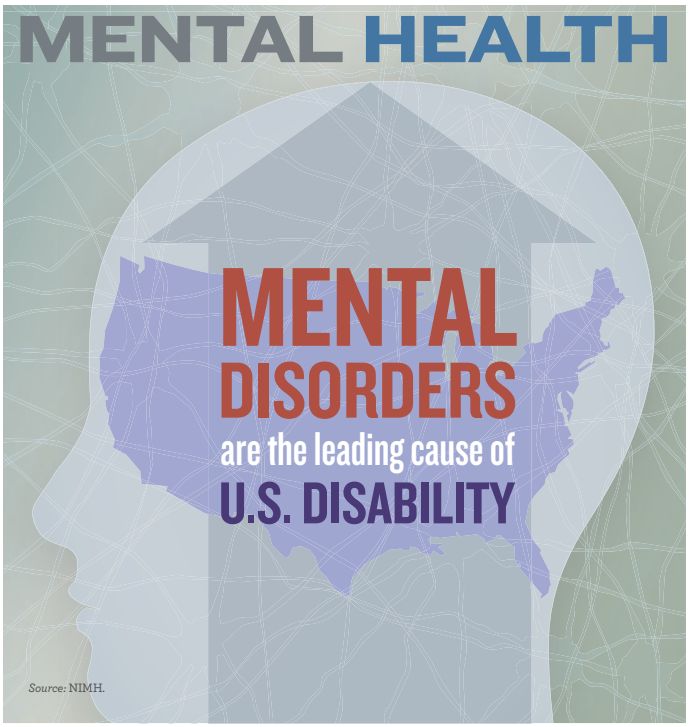
Researching and developing new medicines is a risky investment and lengthy process—only one in 5,000-10,000 targets are ever approved for patients. And although advances in our understanding of mental disorders and how to treat them have allowed America's biopharmaceutical companies and other partners in the collaborative ecosystem to conduct cutting-edge research, additional scientific research is needed to reduce the destructive toll of these disorders and allow more people to lead healthier, more productive lives.

Challenges in Mental Health Research

Development of new and effective treatments for mental disorders has been hindered by many factors, including a limited understanding of how current treatments work in the brain; a lack of biomarkers that help clinicians' diagnose accurately, measure disease progression and assess treatment response; and the complexity of mental disorders themselves. In fact, most medicines that are in use today for the treatment of mental disorders have stemmed from and built on compounds that were initially developed many years ago. NIMH's practical guidelines have documented the sometimes limited benefits of current treatments and the need for a new generation of mental health medicines.

Specific challenges associated with developing new treatments for mental disorders include diagnosis based on symptoms rather than underlying pathology. This can make it difficult to ensure that the appropriate participants are included in a clinical trial. For some disorders, such as schizophrenia or autism spectrum disorder (ASD), individuals meeting the diagnostic criteria, may in reality comprise several subgroups, each with different underlying pathologies even though they have similar symptoms. Therefore, the medication under study may be targeting the appropriate mechanism or pathology in only a subset of the clinical trial participants. Even if the medicine is effective in that portion of participants, it may appear to be ineffective because statistical tests assess the entire group. A greater understanding of





mental disorders will help with diagnosis accuracy and ensure clinical trial participants are grouped appropriately.

At NIMH, several initiatives are underway to help advance research into potential new treatments for mental disorders. One project is focused on creating a new framework to classify mental disorders based on observable behavior and neurobiological measures, such as biomarkers. Current classifications are based on clinical observation and patient-reported symptoms. As scientists gain more knowledge of the underlying biologic causes of mental disorders, having a disorder classification framework ready will aid in a faster and more accurate diagnosis, leading to real progress in researching new treatments.

For example, several research collaborations are looking at the human genome to identify potential genetic indicators for schizophrenia and understand the association between different genetic factors and different subpopulations of people diagnosed with the disorder. Such research could lead to the identification of new targets more closely linked to disease pathology versus overall symptoms. In addition, the research has highlighted how difficult it is to find specific markers or targets because some gene variants are associated with multiple mental disorders. Further research is needed to support the research and development efforts of the biopharmaceutical industry.

Medicines in the Pipeline

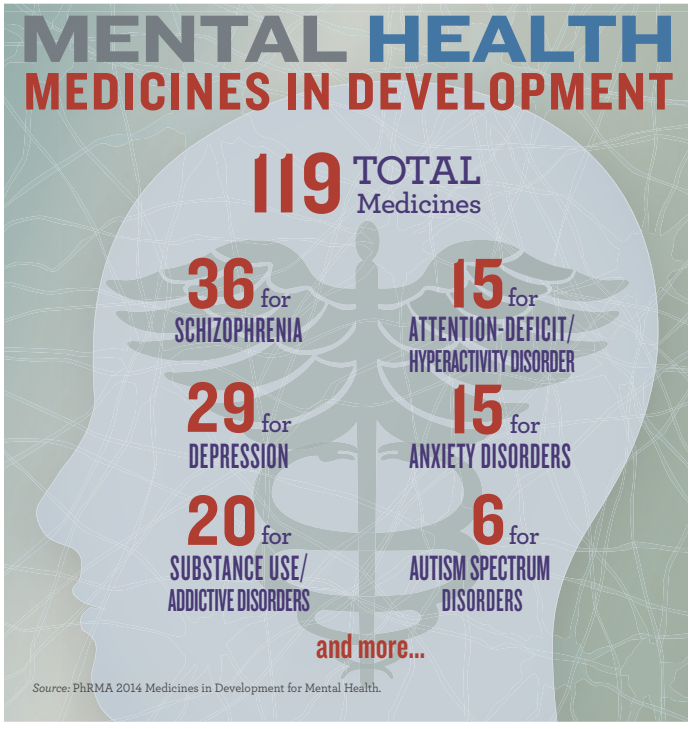
Although research into mental disorders can be very difficult, there are some promising medicines in the pipeline that are looking at new ways to treat many of these disorders. Examples of some current research include:

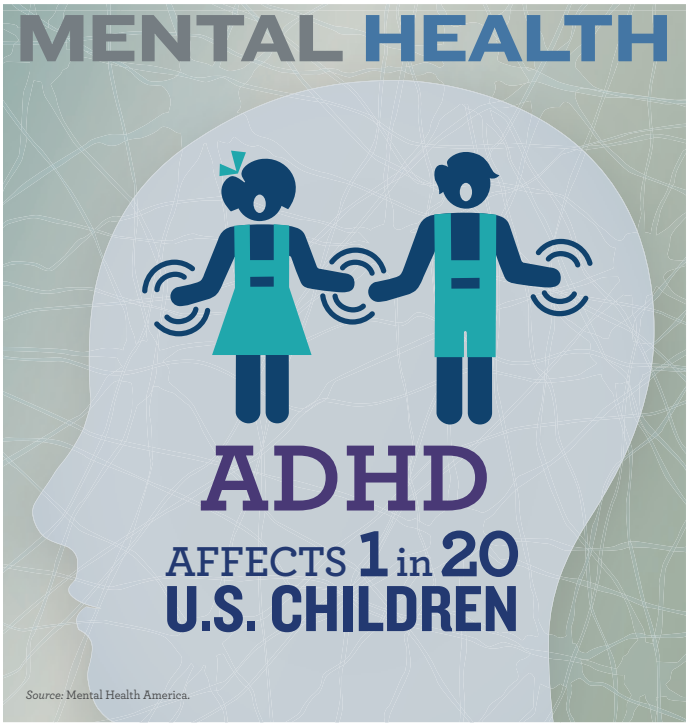
Attention-Deficit/Hyperactivity Disorder (ADHD)

A triple reuptake inhibitor that targets three chemical pathways in brain—serotonin, norepinephrine and dopamine—is being tested for the once-daily treatment of ADHD. By targeting all three pathways at the same time, the compound may potentially provide a broad spectrum of activity. Because of its ability to maintain therapeutic levels in the blood for a long period of time, it is being developed as a once-daily treatment.

Cocaine Addiction

Currently, there are no medications that explicitly address **cocaine addiction**, but a therapeutic vaccine in develop-





ment may prove to be an effective treatment. The vaccine is designed to induce antibodies that bind specifically to cocaine in the blood and prevent it from reaching the brain. The physiological response to cocaine is thus altered, reducing the reinforcing properties of cocaine.

Depression

One medicine in development targets pathways involving glutamate, a common neurotransmitter found in the brain and involved in memory, learning and cognition. Dysfunction of the glutamate system can lead to seizures and cell death and may contribute to some mental disorders. The medicine targets a specific type of glutamate receptor in the brain—the NMDA receptor—resulting in rapid-onset of therapeutic effects—from weeks to hours. An intranasal formulation of the medicine is being developed for **treatment-resistant depression**.

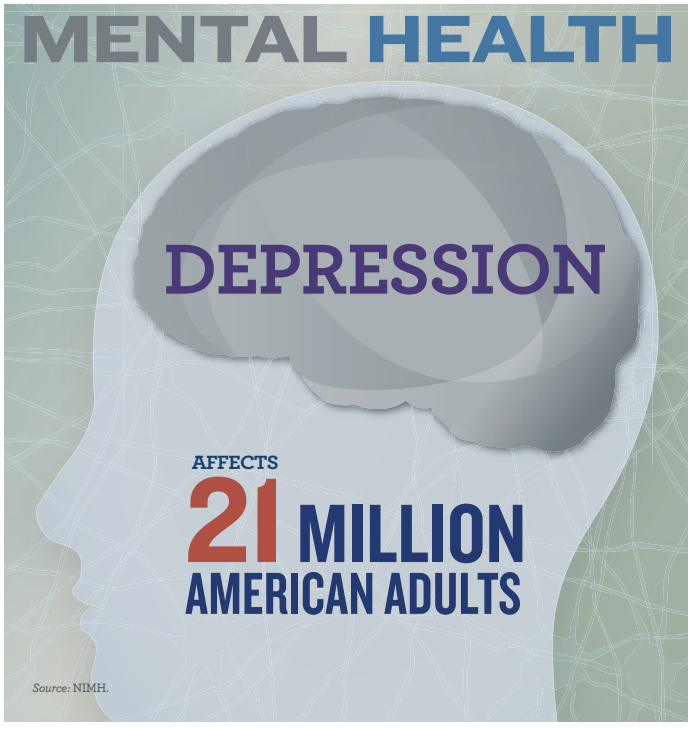
A medicine in development for **major depressive disorder** in patients who have not responded to current treatments combines an opioid modulator with an opioid stimulator. Opioid stimulators have been shown to help in the treatment of depression, but they can also be highly addictive. By coupling the stimulant with an opioid receptor blocker, the addictive qualities are "decoupled" from the antidepressant properties.

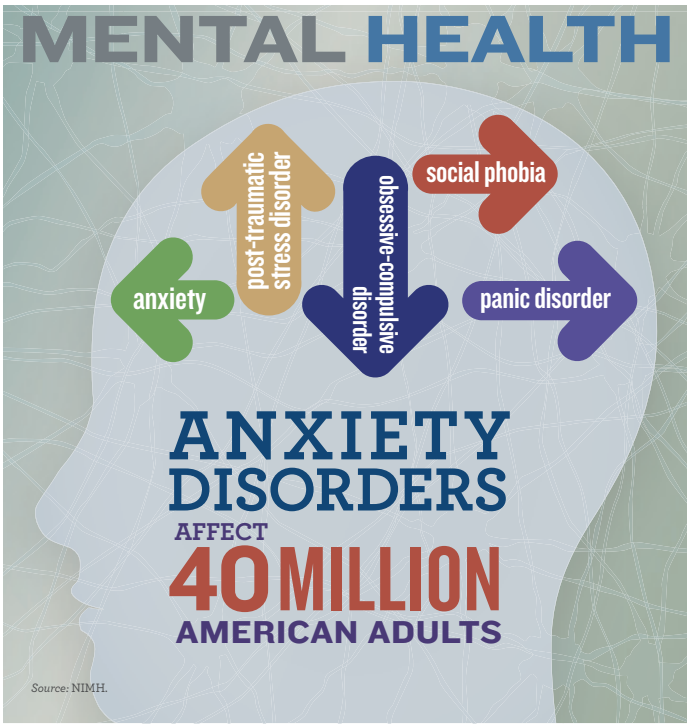
Social Phobia

One medicine in development is part of a new class of psychotropic pherines. The drug, which has a unique mechanism of action, is being developed to be administered in an intranasal spray and to act with rapid-onset on peripheral receptors from nasal chemosensory neurons that act on the hypothalamic-limbic system in the brain, which is thought to be the primary center of emotion. In clinical trials, it was shown to improve social performance and social interaction anxiety within 10 minutes of administration.

Schizophrenia

Several medicines in development for schizophrenia are inhibitors of a subtype of phosphodiesterase (PDE), a key regulator of signaling in the brain. The PDE10 subtype is important in regulating the activity of neurons in the brain and is a target of current antipsychotic treatments. PDE10 inhibitors are highly selective and mimic the effects of current treatments, but also activate certain receptors which may decrease the negative side effects of current treatments and increase the positive effect on cognition.





Collaborative Research Partnerships Are Critical to Advancing Science

Collaboration among partners in the entire biomedical ecosystem is critical to helping advance scientific understanding of brain disorders, one of the most complex areas for researchers. Federal research institutions, academia, biopharmaceutical research companies and patient communities all play an important role in furthering research into those disorders. Some examples of key partnerships include:

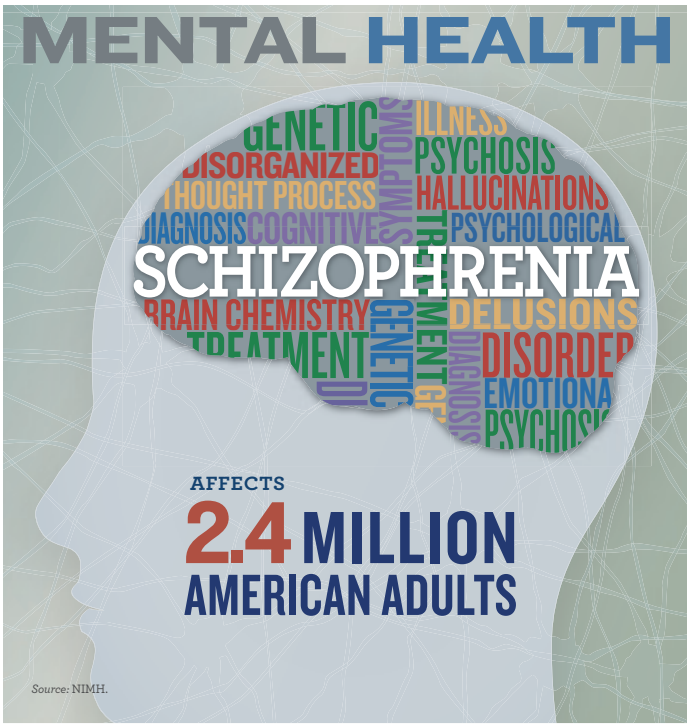
- **One Mind**, a non-profit organization that brings together a broad international coalition of scientists, advocates, philanthropists, government, and the pharmaceutical and health care industries, is dedicated to aiding the acceleration of development of new treatments for brain disorders and injury. The organization's 10-year plan addresses current gaps in basic science, ways to expand translational efforts, and regulatory reforms that are necessary to achieve their mission of cures in the next decade through data sharing, cooperative efforts and public-private partnerships.
- **NEWMEDS** (Novel Methods leading to New Medications in Depression and Schizophrenia) is an international, academic-industry research collaboration dedicated to finding new methods for developing drugs for schizophrenia and depression. NEWMEDS is based in Europe but involves many U.S. industry partners. Ultimately, the goal of NEWMEDS is to develop new approaches for shorter and more efficient trials of new medications, with clinical trials that may require fewer patients and give faster results.

> "We are still at the beginning of what could be an era of brain exploration, with great promise for understanding more about how each of us thinks and dreams and loves, but perhaps even greater promise for helping people with mental disorders."
>
> *—Tom Insel, M.D.*
> *Director, National Institute of Mental Health*

BRAINSPAN ATLAS OF THE DEVELOPING HUMAN BRAIN

The "BrainSpan Atlas" is a comprehensive three-dimensional atlas of the developing human brain that incorporates gene activity along with anatomical reference atlases and neuroimaging data. The Atlas highlights the transcriptome—a map showing when and where genes are turned on in the brain—and anatomy of the human brain during mid-term pregnancy. Some researchers have already had success using the BrainSpan map to associate genes in the developing brain with the adult brain, whereas before they were seemingly unrelated.

The BrainSpan Atlas was developed by a consortium of public and private institutions led by the Allen Institute for Brain Science in Seattle and funded through awards from the NIMH. It is available free to the public and is intended to help researchers better understand mental disorders that may result from changes or problems occurring early during brain development, such as autism and schizophrenia. This understanding may in turn provide new insight into therapeutic targets and improved screening and diagnosis.



- **Fast-Fails Trials (FAST)** is an NIMH program in collaboration with select academic research teams working to accelerate the pace of psychiatric drug discovery through rapid testing of new or repurposed compounds for their potential as psychiatric medications.
- **The Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)** is an unparalleled research study on suicide prevention—a critical area of research for the Army, other military personnel and the general population. The 5-year study, one of the largest and most complex studies ever administered by NIMH, is being conducted in collaboration with select academic research teams.
- The **White House Brain Initiative** (Brain Research through Advancing Innovative Neurotechnologies) is a public-private partnership for brain research focused on increasing our understanding of the human brain by accelerating the development and application of innovative technologies. Through those technologies, researchers will be able to produce a new dynamic picture of the brain that, for the first time, will show how individual cells and complex neural circuits interact in both time and space.

Early Scientific Discoveries

Early-stage research findings are critical for understanding disease pathology and developing new, effective treatments. Many of the challenges in mental health research reflect the reality that we are still learning how the human brain works. Also, research efforts are complicated by the fact that many disorders fall under the broad umbrella of mental health, ranging from anxiety to depression to developmental disorders to substance use disorders. Early scientific discoveries can provide biopharmaceutical companies with potential new treatment pathways for research or for refinement of existing known pathways. Some recent discoveries include:

- The human genome is under examination by research-based institutions around the globe looking for genetic associations in schizophrenia and other mental disorders. Scientists have identified gene variants and mutations in people with schizophrenia and compared them to healthy people, identifying the location and patterns of the mutations. Scientists are optimistic that those discoveries will reveal clues about the underlying biology of schizophrenia.

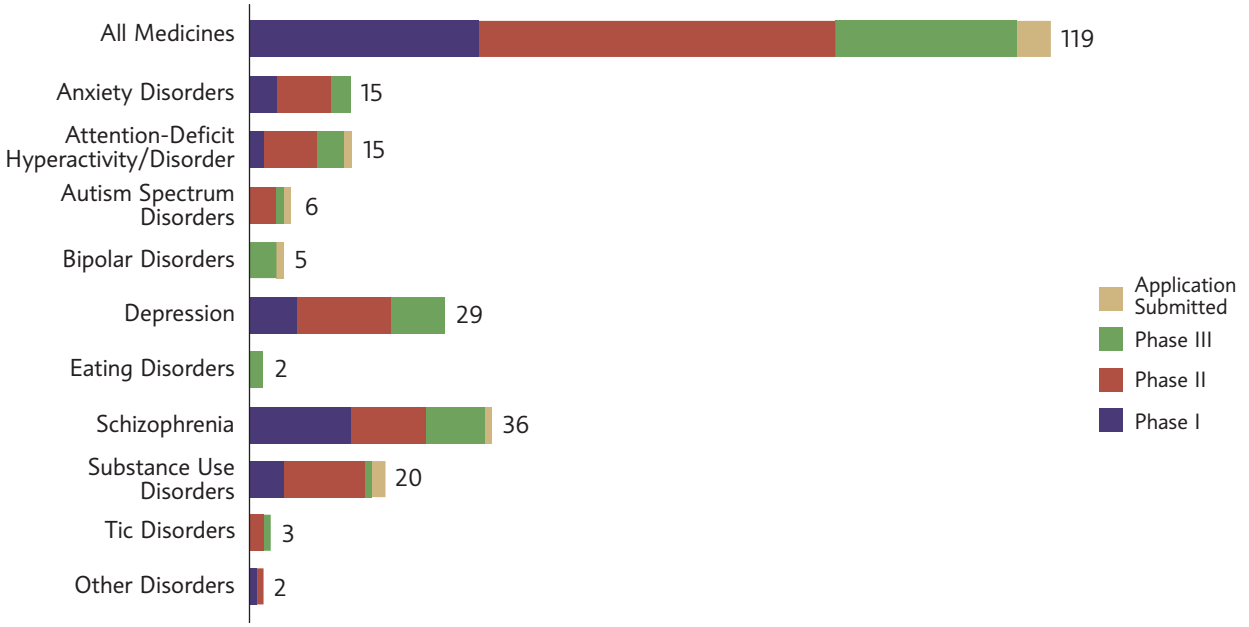
- New data from a team of researchers from Emory University, the University of Miami, and Scripps Research Institute have identified a potential new treatment for post-traumatic stress disorder (PTSD). In mice, the compound reduced PTSD-like symptoms after the animals were exposed to stress. Researchers believe the compound affects the fear learning process. Such findings could potentially lead to a treatment that could prevent PTSD after an individual is exposed to a psychologically traumatic event.
- New research from Oregon Health & Science University's Vollum Institute is giving scientists a "never-before-seen" view of how nerve cells communicate with each other and possibly a better understanding of how antidepressants work in the human brain. Using special methods, scientists focused on the structure of the dopamine transporter, which helps regulate dopamine levels in the brain—abnormal levels of dopamine are present in many disorders, including depression. The more detailed view and understanding of the dopamine transporter could help biopharmaceutical researchers develop more effective antidepressants.

ADHERENCE TO TREATMENT CAN IMPROVE HEALTH OUTCOMES AND COSTS

Adherence to medication dosing and scheduling is important to treat mental health conditions effectively and help control costs by limiting relapses, hospitalizations and limiting indirect costs like lost productivity. Data highlighted by the American Pharmacists Association estimated that nonadherence rates are between 30 percent and 65 percent in individuals diagnosed with a severe mental illness. Many barriers to adherence have been identified, including patient and family attitudes, treatment-related issues (side effects), health system factors, cultural influences, and the perceived stigma associated with mental disorders.

Medicines in Development By Disease and Phase

Some medicines are listed in more than one category.



Selected Facts about Mental Health in the United States

Overview[1]

- An estimated 61.5 million Americans—about one in four adults—suffer from a diagnosable **mental disorder** in a given year. About 13.6 million Americans, or 1 in 17, suffer from a serious mental illness.
- About 20 percent of young Americans ages 13 to 18 and 13 percent of those ages 8 to 15 experience severe **mental disorders** in a given year.
- Mental disorders are the leading cause of **disability** in the United States. Many people suffer from more than one mental disorder at a given time. Nearly half (45 percent) of those with any mental disorder meet criteria for two or more disorders.
- In 2011, **suicide** was the tenth leading cause of death in the United States, accounting for 38,285 deaths. Risk factors for suicide include **depression** and other **mental disorders** or a **substance use disorder** (often in combination with other mental disorders).
- Serious mental illnesses cost the United States more than $317 billion annually in **lost wages**, **health care expenditures**, and **disability benefits**. Lost earnings alone account for $193 billion per year.

Co-occurrence/Comorbidity in Mental Health

- Treatment challenges are exacerbated by **co-occurrence** or **comorbidity** of mental disorders. One study found that nearly half of individuals seeking treatment for **substance use disorder** meet diagnostic criteria for **PTSD**, and individuals with co-occurring PTSD and substance use disorder tended to have poorer treatment outcomes compared to those without the comorbidity.[2]
- About one-third of people diagnosed with **major depressive disorder** also have **substance use disorder**, and the comorbidity results in a higher risk of suicide and greater social and personal impairment as well as other psychiatric conditions.[2]
- It is estimated that **depression** occurs in 50 percent of patients diagnosed with **schizophrenia**, and about 47 percent have a lifetime diagnosis of comorbid **substance abuse**.[3]

Anxiety Disorders[1]

- **Anxiety disorders**, which include **panic disorder, obsessive-compulsive disorder, PTSD, generalized anxiety disorder, phobias** and **social anxiety disorder**, affect some 40 million adults ages 18 and older, or about 18 percent of people in that age group in a given year.
- **Generalized anxiety disorder** affects about 6.8 million American adults, including twice as many women as men.
- **Obsessive-compulsive disorder** affects about 2.2 million American adults, striking men and women in roughly equal numbers.
- **Panic disorder** affects about 6 million American adults and is twice as common in women as men.
- **PTSD** affects about 7.7 million American adults, but it can occur at any age, including childhood. Women are more likely to develop PTSD than men, and there is some evidence that susceptibility to the disorder may run in families.
- **Social phobia** affects about 15 million American adults. Women and men are equally likely to develop the disorder.

Attention-Deficit/Hyperactivity Disorder (ADHD)

- **ADHD** is the most common mental disorder in children and adolescents.[1] It affects as many as one in every 20 children, and boys are three to four times more likely than girls to experience the disorder.[4] About 4 percent of adults ages 18 to 44 are affected by ADHD.[1]

- Although most children with **ADHD** have normal or above-normal intelligence, 40 percent to 60 percent have serious **learning difficulties**.[4]
- Children and adolescents with **ADHD** are more likely than children without the disorder to suffer from other **mental disorders**.[4]

Autism Spectrum Disorders[5]

- In 2010, about 1 in 68 8-year-olds were identified with **autism spectrum disorder (ASD)**.* The 2010 estimate is roughly 30 percent higher than the estimate for 2008 (1 in 88), 60 percent higher than the estimate for 2006 (1 in 110), and 120 percent higher than the estimates for 2002 and 2000 (1 in 150). (The exact cause of the increase is unknown, but researchers believe some of it may be due to the way children are identified, diagnosed, and served in their local communities.)
- Boys were almost five times more likely to be identified with **ASD** than girls in 2010. About 1 in 42 boys and 1 in 189 girls were identified with ASD.

Depression[1]

- Mood disorders, which include **major depressive disorder**, dysthymic disorder, and **bipolar disorder**, affect nearly 21 million adults, or about 9.5 percent of the U.S. population age 18 and older in a given year.
- **Bipolar disorder** affects approximately 5.7 million American adults, or about 2.6 percent of the U.S. population age 18 and older in a given year. The median age of onset for bipolar disorder is 25 years.
- **Depression** can strike anyone regardless of age, ethnic background, socioeconomic status, or gender; however, studies have found that depression is about twice as common in women as in men. In any given one year period, depressive illnesses affect more than 12 million women and more than 6 million men.
- **Major depressive disorder** is the leading cause of disability among Americans ages 15-44. It affects nearly 15 million U.S. adults.

Eating Disorders[1]

- In their lifetime, an estimated 0.6 percent of the U.S. adult population will suffer from anorexia, 1.0 percent from bulimia, and 2.8 percent from a **binge-eating disorder**.
- Women are much more likely than men to develop an eating disorder. They are three times as likely to experience anorexia (0.9 percent of women vs. 0.3 percent of men) and bulimia (1.5 percent of women vs. 0.5 percent of men) during their lives. They are also 75 percent more likely to have a **binge-eating disorder** (3.5 percent of women vs. 2.0 percent of men).

Schizophrenia

- Approximately 2.4 million American adults age 18 and older have **schizophrenia** in a given year. It affects men and women with equal frequency. Schizophrenia often first appears in men in their late teens or early twenties. In contrast, women are generally affected in their twenties or early thirties.[1]
- The appearance of schizophrenic symptoms before age 12 is rare—less than one-sixtieth as common as the adult-onset type. Neurodevelopmental damage seems to be greater in childhood **schizophrenia** than in the adult-onset type.[5]

Substance Use/Addictive Disorders

- An estimated 17 million Americans have an **alcohol use disorder**—a medical term that includes both alcoholism and harmful drinking that does not reach the level of dependence.[6]
- Each year in the United States, nearly 80,000 people die from **alcohol-related causes**, making it the third leading preventable cause of death in our country.[6]

* Estimates are based on information collected from the health and special education records of 8-year-old children living in areas of 11 different states. They do not represent the entire population of children in the United States.

- **Illicit drug use** in America has been increasing. In 2012, an estimated 23.9 million Americans ages 12 or older—or 9.2 percent of the population—had used an illicit drug or abused a psychotherapeutic medication (such as a pain reliever, stimulant, or tranquilizer) in the past month. That was up from 8.3 percent in 2002.[7]
- In 2008 there were 1.9 million **cocaine** users. Adults ages 18 to 25 have a higher rate of current cocaine use than any other age group. Overall, men report higher rates of cocaine use than women.[8]
- Estimates of the **total overall costs of substance abuse** in the United States, including productivity and health- and crime-related costs, exceed $600 billion annually. That includes approximately $193 billion for **illicit drugs**, $193 billion for **tobacco**, and $235 billion for **alcohol**.[7]

Tourette's Syndrome[9]

- Approximately 1 in 200 children have Tourette's syndrome.

Sources:

1. National Institute of Mental Health, *www.nimh.nih.gov*
2. National Center for Biotechnology Information, *www.ncbi.nlm.nih.gov*
3. Schizophrenia Bulletin, *www.schizophreniabulletin.oxfordjournals.org*
4. Mental Health America, *www.mentalhealthamerica.net*
5. U.S. Centers for Disease Control and Prevention, *www.cdc.gov*
6. National Institute on Alcohol Abuse and Alcoholism, *www.niaaa.nih.gov*
7. National Institute on Drug Abuse, *www.drugabuse.gov*
8. Substance Abuse and Mental Health Services Administration, *www.samhsa.gov*
9. National Alliance on Mental Illness, *www.nami.org*

Anxiety Disorders

Product Name	Sponsor	Indication	Development Phase*
aloradine (sensory receptor cell modulator)	Pherin Pharmaceuticals *Los Altos, CA*	social anxiety disorder (social phobia)	Phase II completed www.pherin.com
alprazolam patch	Nuvo Research *Mississauga, Canada*	panic disorder	Phase I www.nuvoresearch.com
AVN-101 (5-HT6 receptor antagonist)	AllaChem *Hallandale Beach, FL* Avineuro *San Diego, CA*	anxiety	Phase II www.allachem.com www.avineuro.com
AVP-923 (dextromethorphan/quinidine fixed-dose combination)	Avanir *Aliso Viejo, CA*	aggitation in Alzheimer's disease	Phase II www.avanir.com
bitopertin (GlyT1 inhibitor)	Roche *Nutley, NJ*	obsessive-compulsive disorder (see also schizophrenia)	Phase II www.roche.com
brexpiprazole (dopamine partial agonist)	Lundbeck *Deerfield, IL* Otsuka Pharmaceutical *Rockville, MD*	agitation associated with Alzheimer's disease (see also ADHD, depression, schizophrenia) --- post-traumatic stress disorder (PTSD)	Phase III www.lundbeck.com www.otsuka.com --- Phase III www.lundbeck.com www.otsuka.com
Brintellix® vortioxetine	Lundbeck *Deerfield, IL* Takeda Pharmaceuticals *Deerfield, IL*	generalized anxiety disorder (see also depression) --- anxiety disorders (children and adolescents)	Phase III www.lundbeck.com www.takeda.com --- Phase II www.lundbeck.com www.takeda.com
ELND005	Transition Therapeutics *Toronto, Canada*	agitation and aggression associated with Alzheimer's disease (Fast Track)	Phase II www.transitiontherapeutics.com
ganaxolone	Marinus Pharmaceuticals *New Haven, CT*	PTSD	Phase II www.marinuspharma.com
guanfacine extended release (SPD503)	Shire *Wayne, PA*	generalized anxiety disorder separation anxiety disorder, social phobia	Phase II completed www.shire.com

*For more information about a specific medicine or company in the report, please use the website provided.

Anxiety Disorders

Product Name	Sponsor	Indication	Development Phase
IW-2143	Bionomics *Thebarton, Australia* Ironwood Pharmaceuticals *Cambridge, MA*	anxiety	Phase I www.bionomics.com.au www.ironwoodpharma.com
JNJ-42165279	Janssen Research & Development *Raritan, NJ*	anxiety disorders	Phase I www.janssenrnd.com
nepicastat (SYN117)	Biotie Therapies *Turku, Finland* U.S. Department of Defense *Washington, DC*	PTSD (see also substance use)	Phase II www.biotie.com
SRX246 (vasopressin 1a receptor antagonist)	Azevan Pharmaceuticals *Bethlehem, PA*	stress-related affective disorders	Phase I www.azevan.com
Viibryd® vilazodone	Forest Laboratories *New York, NY*	generalized anxiety disorder (see also depression)	Phase III www.frx.com

Attention-Deficit/Hyperactivity Disorder

Product Name	Sponsor	Indication	Development Phase
ADHD therapeutic	Neos Therapeutics *Grand Prairie, TX*	attention-deficit/hyperactivity disorder (ADHD)	in clinical trials www.neostx.com
AR08 (adrenergic receptor agonist)	Arbor Pharmaceuticals *Atlanta, GA*	ADHD	Phase II www.arborpharma.com
ATS (dexamfetamine transdermal)	Noven Pharmaceuticals *Miami, FL*	ADHD	Phase II www.noven.com
brexpiprazole (dopamine partial agonist)	Lundbeck *Deerfield, IL* Otsuka Pharmaceutical *Rockville, MD*	ADHD (adults) (see also anxiety, depression, schizophrenia)	Phase II www.lundbeck.com www.otsuka.com
EB-1020 (triple reuptake inhibitor)	Euthymics Biosciences *Cambridge, MA*	ADHD (adults)	Phase II www.euthymics.com
edivoxetine	Eli Lilly *Indianapolis, IN*	ADHD	Phase II/III www.lilly.com

Attention-Deficit/Hyperactivity Disorder

Product Name	Sponsor	Indication	Development Phase
eltoprazine	Amarantus Bioscience *San Francisco, CA*	ADHD (adults)	Phase II www.amarantus.com
HLD200 (methylphenidate modified release)	Highland Therapeutics *Toronto, Canada* Ironshore Pharmaceuticals and Development *Toronto, Canada*	ADHD (pediatric)	Phase III www.highlandtherapeutics.com
metadoxine extended release	Alcobra *Tel-Aviv, Israel*	ADHD (adults)	Phase II/III www.alcobra-pharma.com
NT0102	Neos Therapeutics *Grand Prairie, TX*	ADHD (pediatric)	Phase III www.neostx.com
NT0202 (amphetamine polistirex disintegrating tablet, extended release)	Neos Therapeutics *Grand Prairie, TX*	ADHD	application submitted www.neostx.com
ORADUR®-ADHD methylphenidate sustained release	DURECT *Cupertino, CA*	ADHD	Phase I www.durect.com
SEP-225289 (triple reuptake inhibitor)	Sunovion *Marlborough, MA*	ADHD	Phase II www.sunovion.com
SPN-810 (molindone)	Supernus Pharmaceuticals *Rockville, MD*	impulsive aggression in ADHD	Phase II completed www.supernus.com
SPN-812 (adrenergic uptake inhibitor)	Supernus Pharmaceuticals *Rockville, MD*	ADHD (adults)	Phase II completed www.supernus.com

Autism Spectrum Disorders

Autism spectrum disorders, although most commonly referred to as developmental disorders, are included here because individuals with autism can have mental health-related symptoms.

Product Name	Sponsor	Indication	Development Phase
AT001 (fluoxetine rapid dissolve) ORPHAN DRUG	Autism Therapeutics *New York, NY*	autism (repetitive behaviors) (Fast Track)	Phase III www.autismtherapeutics.com
CM-AT	Curemark *Rye, NY*	autism (Fast Track)	application submitted www.curemark.com

Autism Spectrum Disorders

Product Name	Sponsor	Indication	Development Phase
CNDO-201 (*Trichuris suis* ova)	Coronado Biosciences *Burlington, MA*	autism	Phase II www.coronadobiosciences.com
memantine	Forest Laboratories *New York, NY*	pervasive developmental disorder not otherwise specified, Asperger's syndrome, autism (pediatric)	Phase II completed www.frx.com
RG7314 (vasopressin-1 receptor antagonist)	Roche *Nutley, NJ*	autism	Phase II www.roche.com
syntocinon nasal spray	Retrophin *New York, NY*	autism (see also schizophrenia)	Phase II www.retrophin.com

Bipolar Disorders

Product Name	Sponsor	Indication	Development Phase
Abilify® Maintena® aripiprazole for extended release injectable suspension (depot injection)	Otsuka Pharmaceutical *Rockville, MD*	bipolar disorder	Phase III www.otsuka.com
cariprazine	Forest Laboratories *New York, NY*	manic or mixed episodes associated with bipolar I disorder (see also depression, schizophrenia)	application submitted www.frx.com
Latuda® lurasidone	Sunovion *Marlborough, MA*	bipolar maintenance (see also depression)	Phase III www.sunovion.com
Rozerem® ramelteon (sublingual formulation)	Takeda Pharmaceutical *Deerfield, IL*	bipolar 1 disorder	Phase III www.takeda.com
Saphris® asenapine	Forest Laboratories *New York, NY* Merck *Whitehouse Station, NJ*	bipolar disorder (children and adolescents)	Phase III www.frx.com www.merck.com

Depression

Product Name	Sponsor	Indication	Development Phase
ademetionine (MSI-195)	MSI Methylation Sciences *Burnaby, Canada*	major depressive disorder	Phase II www.methylationsciences.com
ALKS 5461 (buprenorphine/samidorphan)	Alkermes *Waltham, MA*	major depressive disorder (Fast Track)	Phase III www.alkermes.com
amitifadine (triple reuptake inhibitor)	Euthymics Bioscience *Cambridge, MA*	major depressive disorder	Phase II/III www.euthymics.com
armodafinil	Teva Pharmaceutical *North Wales, PA*	major depressive disorder associated with bipolar 1 disorder (see also eating disorders)	Phase III completed www.tevapharm.com
AVP-786 (deuterium modified dextromethorphan and ultra-low dose quinidine)	Avanir Pharmaceuticals *Aliso Viejo, CA* Concert Pharmaceuticals *Lexington, MA*	treatment-resistant depression	Phase I completed www.avanir.com www.concertpharma.com
AZD6423 (NMDA modulator)	AstraZeneca *Wilmington, DE*	suicidal ideation	Phase I www.astrazeneca.com
Botox® onabotulinumtoxinA	Allergan *Irvine, CA*	major depressive disorder	Phase II www.allergan.com
brexpiprazole (dopamine partial agonist)	Lundbeck *Deerfield, IL* Otsuka Pharmaceutical *Rockville, MD*	major depressive disorder (adjunctive treatment) (see also ADHD, anxiety, schizophrenia)	Phase III www.lundbeck.com www.otsuka.com
Brintellix® vortioxetine	Lundbeck *Deerfield, IL* Takeda Pharmaceutical *Deerfield, IL*	depressive disorders (children and adolescents) (see also anxiety)	Phase II www.lundbeck.com www.takeda.com
cariprazine	Forest Laboratories *New York, NY*	bipolar depression, major depressive disorder (adjunctive treatment) (see also bipolar, schizophrenia)	Phase II www.frx.com
CERC-301 (NR2B antagonist)	Cerecor *Baltimore, MD*	major depressive disorder (Fast Track) --- active suicidal ideation	Phase II www.cerecor.com --- Phase II www.cerecor.com
DSP-1053 (serotonin uptake inhibitor)	Sunovion *Marlborough, MA*	major depressive disorder	Phase I www.sunovion.com

Depression

Product Name	Sponsor	Indication	Development Phase
esketamine (intranasal)	Janssen Research & Development *Raritan, NJ*	treatment-resistant major depressive disorder (Fast Track)	Phase II www.janssenrnd.com
GLYX-13	Naurex *Evanston, IL*	major depressive disorder (Fast Track)	Phase II www.naurex.com
HT-2157 (GALR3 antagonist)	Dart NeuroScience *San Diego, CA*	major depressive disorder	Phase II www.dartneuroscience.com
JNJ-42847922	Janssen Research & Development *Raritan, NJ*	major depressive disorder	Phase I www.janssenrnd.com
Latuda® lurasidone	Sunovion *Marlborough, MA*	major depressive disorder with mixed features (see also bipolar)	Phase III www.sunovion.com
LY03005	Luye America Pharmaceuticals *Princeton, NJ*	major depressive disorder	Phase I www.luye.cn
LY2940094 (NOC-1 antagonist)	Eli Lilly *Indianapolis, IN*	major depressive disorder (see also substance use)	Phase II www.lilly.com
mifepristone	Corcept Therapeutics *Menlo Park, CA*	major depression disorder with psychotic features	Phase III www.corcept.com
MIN-117 (5-HT1A/5-HTT receptor antagonist)	Minerva Neurosciences *Cambridge, MA*	major depressive disorder	Phase II www.minervaneurosciences.com
NRX-1074 (NMDA receptor agonist)	Naurex *Evanston, IL*	major depressive disorder	Phase I www.naurex.com
NSI-189 (stimulating neurogenesis)	Neuralstem *Germantown, MD*	major depressive disorder	Phase I www.neuralstem.com
Pristiq® desvenlafaxine	Pfizer *New York, NY*	major depressive disorder (children and adolescents)	Phase III www.pfizer.com
RG1578 (mGluR2)	Roche *Nutley, NJ*	major depressive disorder	Phase II www.roche.com
RG7090 (mGluR5 antagonist)	Roche *Nutley, NJ*	treatment-resistant depression	Phase II www.roche.com

Depression

Product Name	Sponsor	Indication	Development Phase
RO4995819	Roche *Nutley, NJ*	major depressive disorder	Phase II www.roche.com
tedatioxetine	Lundbeck *Deerfield, IL* Takeda Pharmaceutical *Deerfield, IL*	major depressive disorder	Phase II www.lundbeck.com www.takeda.com
Viibryd® vilazodone	Forest Laboratories *New York, NY*	major depressive disorder (adolescents) (see also anxiety)	Phase III www.frx.com

Eating Disorders

Product Name	Sponsor	Indication	Development Phase
armodafinil	Teva Pharmaceutical *North Wales, PA* Lindner Center of HOPE *Cincinnati, OH*	binge-eating disorder (see also depression)	Phase III www.tevapharm.com
LDX (lisdexamfetamine)	Shire *Wayne, PA*	binge-eating disorder (adults)	Phase III www.shire.com

Schizophrenia

Product Name	Sponsor	Indication	Development Phase
ABT-126 (alpha7 NNR antagonist)	AbbVie *North Chicago, IL*	cognition impairment associated with schizophrenia (CIAS)	Phase II www.abbvie.com
ADX71149/JNJ-40411813 (mGlu2 PAM modulator)	Addex Therapeutics *Geneva, Switzerland* Janssen Research & Development *Raritan, NJ*	schizophrenia	Phase II www.addextherapeutics.com www.janssenrnd.com
ALKS 3831 (olanzapine/samidorphan fixed-dose combination)	Alkermes *Waltham, MA*	schizophrenia	Phase II www.alkermes.com
AMG 581	Amgen *Thousand Oaks, CA*	schizophrenia	Phase I www.amgen.com

Schizophrenia

Product Name	Sponsor	Indication	Development Phase
AQW051 (alpha7 nicotinic acetylcholine receptor agonist)	Novartis Pharmaceuticals *East Hanover, NJ*	CIAS	Phase II completed www.novartis.com
aripiprazole lauroxil (ALKS 9072)	Alkermes *Waltham, MA*	schizophrenia	Phase III www.alkermes.com
AVL-3288 (alpha7 nicotinic acetylcholine receptor modulator)	Anvyl Pharmaceuticals *Irvine, CA*	CIAS	Phase I www.anvyllc.com
AVN-211 (5-HT6 receptor antagonist)	AllaChem *Hallandale Beach, FL* Avineuro Pharmaceuticals *San Diego, CA*	schizophrenia	Phase II www.allachem.com www.avineuro.com
BI-409306	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	schizophrenia	Phase I completed www.boehringer-ingelheim.com
bitopertin (GlyT1 inhibitor)	Roche *Nutley, NJ*	schizophrenia-suboptimally controlled symptoms (see also anxiety)	Phase III www.roche.com
brexpiprazole (dopamine partial agonist)	Lundbeck *Deerfield, IL* Otsuka Pharmaceutical *Rockville, MD*	schizophrenia (see also ADHD, anxiety, depression)	Phase III www.lundbeck.com www.otsuka.com
cariprazine	Forest Laboratories *New York, NY*	schizophrenia (see also bipolar, depression)	application submitted www.frx.com
CEP-26401 (irdabisant)	Teva Pharmaceutical *North Wales, PA*	CIAS	Phase I completed www.tevapharm.com
encenicline (alpha-7 agonist)	Forum Pharmaceuticals *Watertown, MA*	CIAS	Phase III www.forumpharma.com
FRM-6308 (PDE10 inhibitor)	Forum Pharmaceuticals *Watertown, MA*	schizophrenia	Phase I www.forumpharma.vom
Invega® Sustenna® paliperidone palmitate	Alkermes *Waltham, MA* Janssen Research & Development *Raritan, NJ*	schizoaffective disorder ---------- schizophrenia (3 month injectable)	Phase III www.alkermes.com www.janssenrnd.com ---------- Phase III www.alkermes.com www.janssenrnd.com

Schizophrenia

Product Name	Sponsor	Indication	Development Phase
ITI-007 (5-HT2A serotonin receptor antagonist)	Intra-Cellular Therapies *New York, NY*	schizophrenia	Phase II www.intracellulartherapies.com
ITI-214 (PDE1 inhibitor)	Intra-Cellular Therapies *New York, NY* Takeda Pharmaceuticals *Deerfield, IL*	CIAS	Phase I www.intracellulartherapies.com www.takeda.com
LY03004 (risperidone controlled release)	Luye America Pharmaceuticals *Princeton, NJ*	schizophrenia, schizoaffective disorder	Phase I www.luye.cn
MIN-101 (5-HT2A/sigma-2 receptor antagonist)	Minerva Neurosciences *Cambridge, MA*	schizophrenia	Phase II www.minervaneurosciences.com
NW-3509 (potent sodium channel blocker)	Newron Pharmaceuticals *Bresso, Italy*	schizophrenia	Phase I www.newron.com
OMS824 (PDE10 inhibitor)	Omeros *Seattle, WA*	schizophrenia	Phase II www.omeros.com
PF-02545920 (PDE10 inhibitor)	Pfizer *New York, NY*	schizophrenia (adjunctive treatment)	Phase II www.pfizer.com
PF-04958242 (AMPA receptor modulator)	Pfizer *New York, NY*	schizophrenia	Phase I www.pfizer.com
PF-06412562	Pfizer *New York, NY*	CAIS	Phase I www.pfizer.com
pimavanserin	ACADIA Pharmaceuticals *San Diego, CA*	Parkinson's disease psychosis --- Alzheimer's disease psychosis, schizophrenia	Phase III www.acadia-pharm.com --- Phase II www.acadia-pharm.com
RBP-7000 (dopamine-D2/serotonin-2 antagonist)	Reckitt Benckiser Pharmaceutical *Richmond, VA*	schizophrenia	Phase III www.rb.com
Relday™ risperidone controlled release	DURECT *Cupertino, CA* Zogenix *San Diego, CA*	schizophrenia	Phase I www.durect.com www.zogenix.com

Schizophrenia

Product Name	Sponsor	Indication	Development Phase
RG7203 (PDE10A inhibitor)	Roche *Nutley, NJ*	schizophrenia	Phase I www.roche.com
RO5545965	Roche *Nutley, NJ*	schizophrenia	Phase I www.roche.com
RP5063 (partial agonist of dopamine and serotonin)	Reviva Pharmaceuticals *San Jose, CA*	schizophrenia, schizoaffective disorder	Phase II www.revivapharma.com
Saphris® asenapine	Forest Laboratories *New York, NY* Merck *Whitehouse Station, NJ*	schizophrenia (adolescents) (see also bipolar)	Phase III completed www.frx.com www.merck.com
SEP-363856	Sunovion *Marlborough, MA*	schizophrenia	Phase I www.sunovion.com
syntocinon nasal spray	Retrophin *New York, NY*	schizophrenia (see also autism)	Phase II www.retrophin.com
TAK-063 (PDE10A inhibitor)	Takeda Pharmaceuticals *Deerfield, IL*	schizophrenia	Phase I www.takeda.com
zicronapine	Lundbeck *Deerfield, IL*	schizophrenia	Phase III www.lundbeck.com

Substance Use/Addictive Disorders

Product Name	Sponsor	Indication	Development Phase
ABT-436 (selective vasopressin receptor antagonist)	AbbVie *North Chicago, IL* National Institute on Alcohol Abuse and Alcoholism *Bethesda, MD*	alcohol use disorder	Phase II www.abbvie.com www.niaaa.nih.gov
AD01 (ondansetron/topiramate)	ADial Pharmaceuticals *Charlottesville, VA*	alcohol use disorder	Phase II www.adialpharma.com
AD04 (low-dose ondansetron)	ADial Pharmaceuticals *Charlottesville, VA*	alcohol use disorder	Phase II www.adialpharma.com
Bunavail™ buprenorphine/naloxone transmucosal	BioDelivery Sciences International *Raleigh, NC*	opioid use disorder, opioid abuse	application submitted www.bdsi.com

Substance Use/Addictive Disorders

Product Name	Sponsor	Indication	Development Phase
bupropion/mecamylamine once-daily tablet (QuitPak®)	Cary Pharmaceuticals *Great Falls, VA*	smoking withdrawal	Phase I completed www.carypharma.com
Ch-mAb7F9 (METH-mAb)	InterveXion Therapeutics *Little Rock, AR*	methamphetamine use disorder	Phase I completed www.intervexion.com
EMB-001 (metyrapone/oxazepam)	Embera NeuroTherapeutics *Sudbury, MA*	cocaine use disorder	Phase I completed www.emberaneuro.com
lofexidine	US WorldMeds *Louisville, KY* National Institute on Drug Abuse *Bethesda, MD*	opioid use disorder	Phase III www.usworldmeds.com www.drugabuse.gov
LY2940094 (NOC-1 antagonist)	Eli Lilly *Indianapolis, IN*	alcohol use disorder (see also depression)	Phase II www.lilly.com
MN-166 (ibudilast)	MediciNova *La Jolla, CA* National Institute on Drug Abuse *Bethesda, MD*	methamphetamine use disorder (Fast Track)	Phase II www.medicinova.com www.drugabuse.gov
naloxone nasal spray	Lightlake Therapeutics *London, United Kingdom* National Institute on Drug Abuse *Bethesda, MD*	opioid use disorder	Phase II www.lightlaketherapeutics.com www.drugabuse.gov
nepicastat (SYN117)	Biotie Therapies *Turku, Finland* National Institute on Drug Abuse *Bethesda, MD*	cocaine use disorder (see also anxiety)	Phase II www.biotie.com www.drugabuse.gov
OMS405 (PPAR-gamma agonist)	Omeros *Seattle, WA*	opioid use disorder, smoking withdrawal	Phase II www.omeros.com
PF-05402536 (smoking cessation vaccine)	Pfizer *New York, NY*	smoking withdrawal	Phase I www.pfizer.com
Probuphine® buprenorphine implant	Braeburn Pharmaceuticals *Princeton, NJ* Titan Pharmaceuticals *South San Francisco, CA*	opioid use disorder	application submitted www.braeburnpharmaceuticals.com www.titanpharm.com
RBP-6000 (buprenorphine depot)	Reckitt Benckiser Pharmaceutical *Richmond, VA*	opioid use disorder	Phase II www.rb.com

Substance Use/Addictive Disorders

Product Name	Sponsor	Indication	Development Phase
RBP-8000 (cocaine esterase)	Reckitt Benckiser Pharmaceutical *Richmond, VA*	cocaine use disorder	Phase II www.rb.com
SEL-068 (nicotine antibodies)	Selecta Biosciences *Watertown, MA*	smoking withdrawal	Phase I www.selectabio.com
TA-CD (cocaine abuse vaccine)	Baylor College of Medicine *Houston, Texas* Celtic Pharma Holdings *Hamilton, Bermuda* National Institute on Drug Abuse *Bethesda, MD*	cocaine use disorder	Phase II www.drugabuse.gov
TV-1380 (form of human plasma butyrylcholinesterase)	Teva Pharmaceutical *North Wales, PA*	cocaine use disorders	Phase II www.tevapharm.com

TIC Disorders

Product Name	Sponsor	Indication	Development Phase
Abilify® aripiprazole (once-weekly tablet)	Otsuka Pharmaceutical *Rockville, MD*	Tourette's syndrome	Phase III www.otsuka.com
AZD5213 (histamine-3 receptor antagonist)	AstraZeneca *Wilmington, DE*	Tourette's syndrome	Phase II www.astrazeneca.com
ecopipam	Psyadon Pharmaceuticals *Germantown, MD*	Tourette's syndrome	Phase II www.psyadonrx.com

Other Disorders

Product Name	Sponsor	Indication	Development Phase
PH80-PMD	Pherin Pharmaceuticals *Los Altos, CA*	premenstrual dysphoric disorder, premenstrual syndrome	Phase II completed www.pherin.com
RG1662 (GABA-A alpha5 receptor modulator)	Roche *Nutley, NJ*	cognitive impairment associated with Downs syndrome	Phase I www.roche.com

The content of this report has been obtained through public, government and industry sources, and the Adis "R&D Insight" database based on the latest information. **Report current as of April 28, 2014.** *The medicines in this report include medicines being developed by U.S.-based companies conducting trials in the United States and abroad, PhRMA-member companies conducting trials in the United States and abroad, and foreign companies conducting clinical trials in the United States. The information in this report may not be comprehensive. For more specific information about a particular product, contact the individual company directly or go to* ***www.clinicaltrials.gov****. The entire series of Medicines in Development is available on PhRMA's website.*

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Glossary

anxiety disorders—Anxiety is a normal reaction to stress and can be beneficial in some situations, but for some people anxiety may become excessive. While people suffering may realize their anxiety is too much, they may also have difficulty controlling it, and it may negatively affect their day-to-day living. The wide variety of anxiety disorders includes **generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder, post-traumatic stress disorder (PTSD)**, and **social phobia**. Collectively, they are among the most common mental health disorders experienced by Americans.

application submitted—An application for marketing has been submitted by the company to the U.S. Food and Drug Administration (FDA).

attention deficit/hyperactivity disorder (ADHD)—ADHD is a problem of not being able to focus, being overactive, not being able control behavior, or a combination of these symptoms. For those problems to be diagnosed as ADHD, they must be out of the normal range for a person's age and development. ADHD usually begins in childhood but may continue into the adult years. It is the most commonly diagnosed behavioral disorder in children. ADHD is diagnosed much more often in boys than in girls. A combination of genes and environmental factors likely plays a role in the development of the condition. Symptoms of ADHD fall into three groups: not being able to focus (inattentiveness); being extremely active (hyperactivity); and not being able to control behavior (impulsivity). Some people with ADHD have mainly inattentive symptoms. Some have mainly hyperactive and impulsive symptoms. Others have a combination of different symptom types. Those with mostly inattentive symptoms are sometimes said to have attention deficit disorder (ADD). They tend to be less disruptive and are more likely not to be diagnosed with ADHD.

autism spectrum disorder (ASD)—ASD is a developmental disability that can cause significant social, communication and behavioral challenges. People with ASD may communicate, interact, behave, and learn in ways that are different from most other people. The learning, thinking, and problem-solving abilities of people with ASD can range from gifted to severely challenged. Some people with ASD need a lot of help in their daily lives; others need less. People with ASD often have problems with social, emotional, and communication skills. They might repeat certain behaviors and might not want change in their daily activities. Many people with ASD also have different ways of learning, paying attention, or reacting to things. Signs of ASD begin during early childhood and typically last throughout a person's life. A diagnosis of ASD now includes several conditions that used to be diagnosed separately: autistic disorder, pervasive developmental disorder not otherwise specified, and **Asperger's syndrome**. Those conditions are now all called autism spectrum disorder.

binge-eating disorder—With binge-eating disorder a person loses control over his or her eating. Unlike bulimia nervosa, periods of binge-eating are not followed by purging, excessive exercise, or fasting. As a result, people with binge-eating disorder often are overweight or obese. People with binge-eating disorder who are obese are at higher risk for developing cardiovascular disease and high blood pressure. They also experience guilt, shame, and distress about their binge-eating, which can lead to more binge-eating.

bipolar disorder—Also known as manic-depressive illness, a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. Symptoms of bipolar disorder are severe. They are different from the normal ups and downs that everyone goes through from time to time. People with bipolar disorder experience unusually intense emotional states that occur in distinct periods called "mood episodes." Each mood episode represents a drastic change from a person's usual mood and behavior. An overly joyful or overexcited state is called a *manic episode*, and an extremely sad or hopeless state is called a *depressive episode*. Sometimes, a mood episode includes symptoms of both mania and depression, called a *mixed state*. People with bipolar disorder also may be explosive and irritable during a mood episode. Extreme changes in energy, activity, sleep, and behavior go along with those changes in mood. Bipolar disorder symptoms can result in damaged relationships, poor job or school performance, and even suicide. But bipolar disorder can be treated, and people with the illness can lead full and productive lives.

depression—Everyone occasionally feels blue or sad, but those feelings are usually short-lived and pass within a couple of days. Depression, however, interferes with daily life and causes pain for both the sufferers and those who care about them. Depression is a common but serious illness. Major depression and persistent depressive disorder are among the

several forms of depressive disorders. **Major depression** causes severe symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy life. An episode can occur only once in a person's lifetime, but more often, a person has several episodes. **Persistent depressive disorder** causes a depressed mood that lasts for at least 2 years. A person diagnosed with persistent depressive disorder may have episodes of major depression along with periods of less severe symptoms, but symptoms must last for 2 years. People with depressive illnesses do not all experience the same symptoms. The severity, frequency, and duration of symptoms vary depending on the individual and his or her particular illness. A few of the many signs and symptoms of depression are: persistent sad, anxious, or "empty" feelings; feelings of hopelessness or pessimism; fatigue and decreased energy; difficulty concentrating, remembering details, and making decisions; overeating, or appetite loss; and thoughts of suicide, or suicide attempts.

Fast Track—A process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need. The status is assigned by the U.S. Food and Drug Administration (FDA). The purpose of this process is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious diseases. In general, determining factors for whether a drug receives Fast Track include whether the drug will affect factors such as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy that may be potentially superior to existing therapy. Once a drug receives Fast Track designation, early and frequent communication between the FDA and a drug company is encouraged throughout the entire drug development and review process. The frequency of communication ensures that questions and issues are resolved quickly, often leading to earlier drug approval and access by patients.

generalized anxiety disorder (GAD)—While everyone worries about things like health, money, or family problems, people with GAD are extremely worried about those problems and many other things, even when there is little or no reason to worry about them. They are very anxious about just getting through the day, thinking that things will always go badly. At times, worrying keeps people with GAD from doing everyday tasks. They can't relax, startle easily, and have difficulty concentrating. Often they have trouble falling asleep or staying asleep. Physical symptoms that often accompany the anxiety include fatigue, headaches, muscle tension, muscle aches, difficulty swallowing, trembling, twitching, irritability, sweating, nausea, lightheadedness, having to go to the bathroom frequently, feeling out of breath, and hot flashes.

NCE—New chemical entity.

obsessive-compulsive disorder (OCD)—People with OCD feel the need to check things repeatedly or have certain thoughts or perform routines and rituals over and over. The thoughts and rituals associated with OCD cause distress and get in the way of daily life. The frequent upsetting thoughts are called *obsessions*. To try to control them, a person will feel an overwhelming urge to repeat certain rituals or behaviors called *compulsions*. People with OCD can't control those obsessions and compulsions—the rituals usually end up controlling them. For example, if people are obsessed with germs or dirt, they may develop a compulsion to wash their hands over and over again. If they develop an obsession with intruders, they may lock and relock their doors many times before going to bed. Performing such rituals is not pleasurable. At best, it produces temporary relief from the anxiety created by obsessive thoughts. People with OCD perform their rituals even though doing so interferes with daily life, and they find the repetition distressing. Although most adults with OCD recognize that what they are doing is senseless, some adults and most children may not realize that their behavior is out of the ordinary.

Orphan Drug—A drug to treat a disease that has a patient population of 200,000 or less in the United States, or a disease that has a patient population of more than 200,000 and a development cost that will not be recovered from sales in the United States.

panic disorder—People with panic disorder have sudden and repeated attacks of fear that last for several minutes. Sometimes symptoms may last longer and are called *panic attacks*. Panic attacks are characterized by a fear of disaster or of losing control even when there is no real danger. A person may also have a strong physical reaction during a panic attack. It may feel like having a heart attack. Panic attacks can occur at any time, and many people with panic disorder worry about and dread the possibility of having another attack. A person with panic disorder may become discouraged and feel ashamed because

he or she cannot carry out normal routines like going to the grocery store or driving. Having panic disorder can also interfere with school or work.

Phase 0—First-in-human trials conducted in accordance with FDA's 2006 guidance on exploratory Investigational New Drug (IND) studies designed to speed development of promising drugs by establishing early whether the tested compound behaves in humans as was anticipated from preclinical studies.

Phase I—Researchers test the drug in a small group of people, usually between 20 and 80 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Phase II—The drug is given to volunteer patients, usually between 100 and 300, to determine whether the drug is effective, identify an optimal dose, and to evaluate further its short-term safety.

Phase III—The drug is given to a larger, more diverse patient population, often involving between 1,000 and 3,000 patients (but sometimes many more thousands), to generate statistically significant evidence to confirm its safety and effectiveness. Phase III studies are the longest studies and usually take place in multiple sites around the world.

post-traumatic stress disorder (PTSD)—When in danger, it's natural to feel afraid. That fear triggers the "fight-or-flight" response as a healthy reaction meant to protect a person from harm. But in PTSD, that reaction is changed or damaged. People who have PTSD may feel stressed or frightened even when they're no longer in danger. PTSD develops after a terrifying ordeal that involved physical harm or the threat of physical harm. The person who develops PTSD may have been the one who was harmed, the harm may have happened to a loved one, or the person may have witnessed a harmful event that happened to loved ones or strangers. PTSD was first brought to public attention in relation to war veterans, but it can result from a variety of traumatic incidents, such as a mugging, rape, being kidnapped or held captive, child abuse, major accidents, or natural disasters such as floods or earthquakes.

schizoaffective disorder—A serious mental illness that affects about one in 100 people. Schizoaffective disorder as a diagnostic entity has features that resemble both schizophrenia and also serious mood (affective) symptoms. A person who has schizoaffective disorder will experience delusions, hallucinations, other symptoms that are characteristic of schizophrenia, and significant disturbances in their mood (e.g., affective symptoms). People who experience more than two weeks of psychotic symptoms in the absence of severe mood disturbances—and then have symptoms of either depression or bipolar disorder—may have schizoaffective disorder. Schizoaffective disorder is thought to be between the bipolar and schizophrenia diagnoses as it has features of both. Depressive symptoms associated with schizoaffective disorder can include—but are not limited to—hopelessness, helplessness, guilt, worthlessness, disrupted appetite, disturbed sleep, inability to concentrate, and depressed mood (with or without suicidal thoughts). Manic (bipolar) symptoms associated with schizoaffective disorder can include increased energy, decreased sleep (or decreased need for sleep), distractibility, fast speech, and increased impulsive behaviors (e.g., sexual activities, drug and alcohol abuse, gambling, or spending large amounts of money). Many of the strategies used to treat both schizophrenia and affective conditions can be employed for this condition, including antipsychotic and mood stabilizing medications, family involvement, psychosocial strategies, self-care peer support, psychotherapy and integrated care for co-occurring substance abuse (when appropriate).

schizophrenia—A chronic, severe, and disabling brain disorder that has affected people throughout history. About 1 percent of Americans have the illness. People with the disorder may hear voices other people don't hear. They may believe other people are reading their minds, controlling their thoughts, or plotting to harm them. That can terrify people with the illness and make them withdrawn or extremely agitated. People with schizophrenia may not make sense when they talk. They may sit for hours without moving or talking. Sometimes people with schizophrenia seem perfectly fine until they talk about what they are really thinking. Families and society are affected by schizophrenia, too. Many people with schizophrenia have difficulty holding a job or caring for themselves, so they rely on others for help. **Cognitive symptoms** are subtle and may be difficult to recognize as part of the disorder. Often, they are detected only when other tests are performed. Cognitive symptoms include the following: poor "executive functioning" (the ability to understand information and use it to make decisions); trouble focusing or paying attention; problems with "working memory" (the ability to use information immediately after learning it). Cognitive symptoms often make it hard

to lead a normal life and earn a living. They can cause great emotional distress. Treatment helps relieve many symptoms of schizophrenia, but most people who have the disorder cope with symptoms throughout their lives.

social phobia (social anxiety disorder)—Social phobia is a strong fear of being judged by others and of being embarrassed. The fear can be so strong that it gets in the way of going to work or school or doing other everyday things. Meeting new people or giving a public speech can make anyone nervous, but people with social phobia worry about such things for weeks before they happen. People with social phobia are afraid of doing common things in front of other people. For example, they might be afraid to sign a check in front of a cashier at the grocery store, or they might be afraid to eat or drink in front of other people. Most people who have social phobia know that they shouldn't be as afraid as they are, but they can't control their fear. For some people, social phobia is a problem only in certain situations, while others have symptoms in almost any social situation.

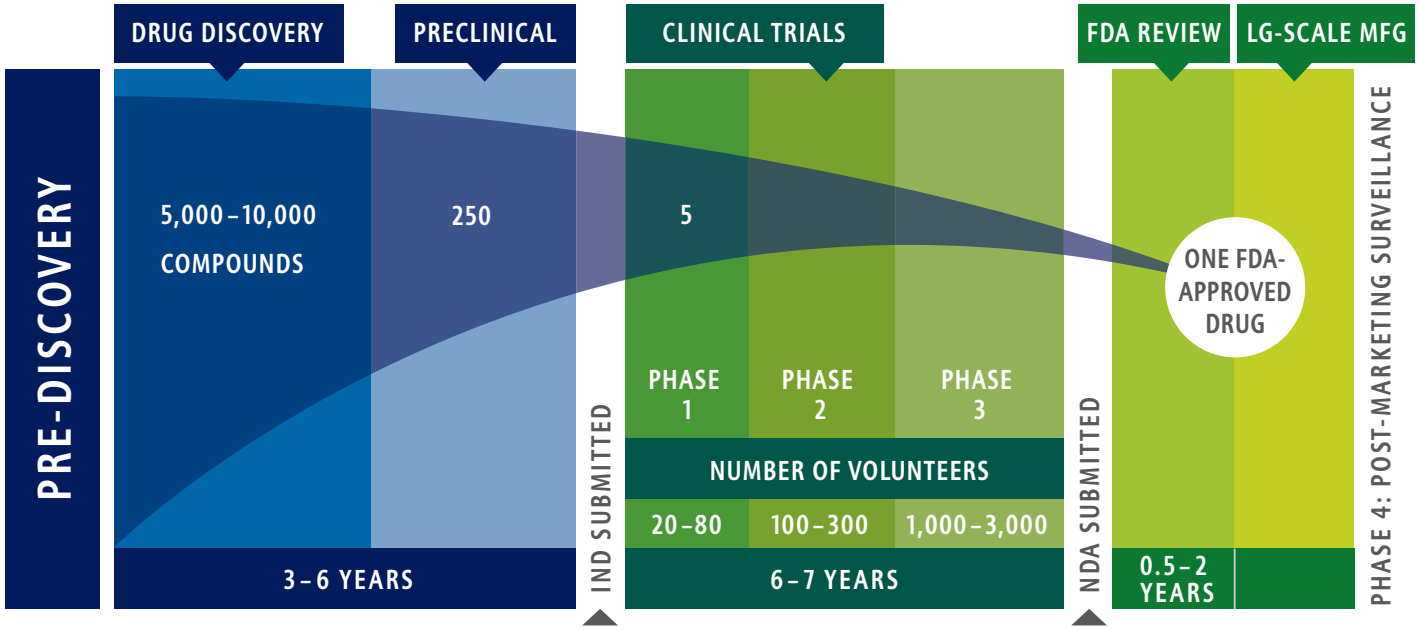
substance use disorders—A term used to characterize illnesses associated with drug use. There are two broad categories: substance abuse and substance dependence. Both are associated with a maladaptive pattern of substance use that leads to clinically significant impairment. Drug abuse includes such symptoms as: failure to fulfill major role obligations; legal problems; use in situations that are physically hazardous; and continued use despite persistent social or interpersonal problems. The term dependence includes such symptoms as: drug taking in larger amounts than intended; inability to cut down on drug use; a great deal of time spent in activities necessary to obtain the drug; and continued use despite knowledge of health or social problems caused by the drug. Dependence may or may not include "physical dependence," defined by withdrawal symptoms when drug use is abruptly ceased, and "tolerance," the need for more of a drug to achieve a desired effect. The term "dependence" can also refer to "addiction." Addiction is defined as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences. It is considered a brain disease because drugs change the brain—its structure and how it works. Those brain changes can be long lasting and can lead to many harmful, often self-destructive, behaviors.

Tourette's syndrome (TS)—A neurological disorder characterized by repetitive, involuntary movements and vocalizations called tics. The early symptoms of TS are typically noticed first in childhood, with the average onset between the ages of 3 and 9. TS occurs in people from all ethnic groups; males are affected about three to four times more often than females. It is estimated that 200,000 Americans have the most severe form of TS, and as many as 1 in 100 exhibit milder and less complex symptoms such as chronic motor or vocal tics. Although TS can be a chronic condition with symptoms lasting a lifetime, most people with the condition experience their worst tic symptoms in their early teens, with improvement occurring in the late teens and continuing into adulthood.

The Drug Discovery, Development and Approval Process

Developing a new medicine takes an average of 10-15 years;
For every 5,000-10,000 compounds in the pipeline, only 1 is approved.

Drug Discovery and Development: A LONG, RISKY ROAD



The Drug Development and Approval Process

The U.S. system of new drug approvals is perhaps the most rigorous in the world.

It takes 10-15 years, on average, for an experimental drug to travel from lab to U.S. patients, according to the Tufts Center for the Study of Drug Development. Only five in 5,000 compounds that enter preclinical testing make it to human testing. And only one of those five is approved for sale.

On average, it costs a company $1.2 billion, including the cost of failures, to get one new medicine from the laboratory to U.S. patients, according to a recent study by the Tufts Center for the Study of Drug Development.

Once a new compound has been identified in the laboratory, medicines are usually developed as follows:

Preclinical Testing. A pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

Investigational New Drug Application (IND). After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration (FDA) to begin to test the drug in people. The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted. Progress reports on clinical trials must be submitted at least annually to FDA and the IRB.

Clinical Trials, Phase I—Researchers test the drug in a small group of people, usually between 20 and 80 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Clinical Trials, Phase II—The drug is given to volunteer patients, usually between 100 and 300, to see if it is effective, identify an optimal dose, and to further evaluate its short-term safety.

Clinical Trials, Phase III—The drug is given to a larger, more diverse patient population, often involving between 1,000 and 3,000 patients (but sometime many more thousands), to generate statistically significant evidence to confirm its safety and effectiveness. They are the longest studies, and usually take place in multiple sites around the world.

New Drug Application (NDA)/Biologic License Application (BLA). Following the completion of all three phases of clinical trials, a company analyzes all of the data and files an NDA or BLA with FDA if the data successfully demonstrate both safety and effectiveness. The applications contain all of the scientific information that the company has gathered. Applications typically run 100,000 pages or more.

Approval. Once FDA approves an NDA or BLA, the new medicine becomes available for physicians to prescribe. A company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional trials (Phase IV) to evaluate long-term effects.

Discovering and developing safe and effective new medicines is a long, difficult, and expensive process. PhRMA member companies invested an estimated $51.1 billion in research and development in 2013.