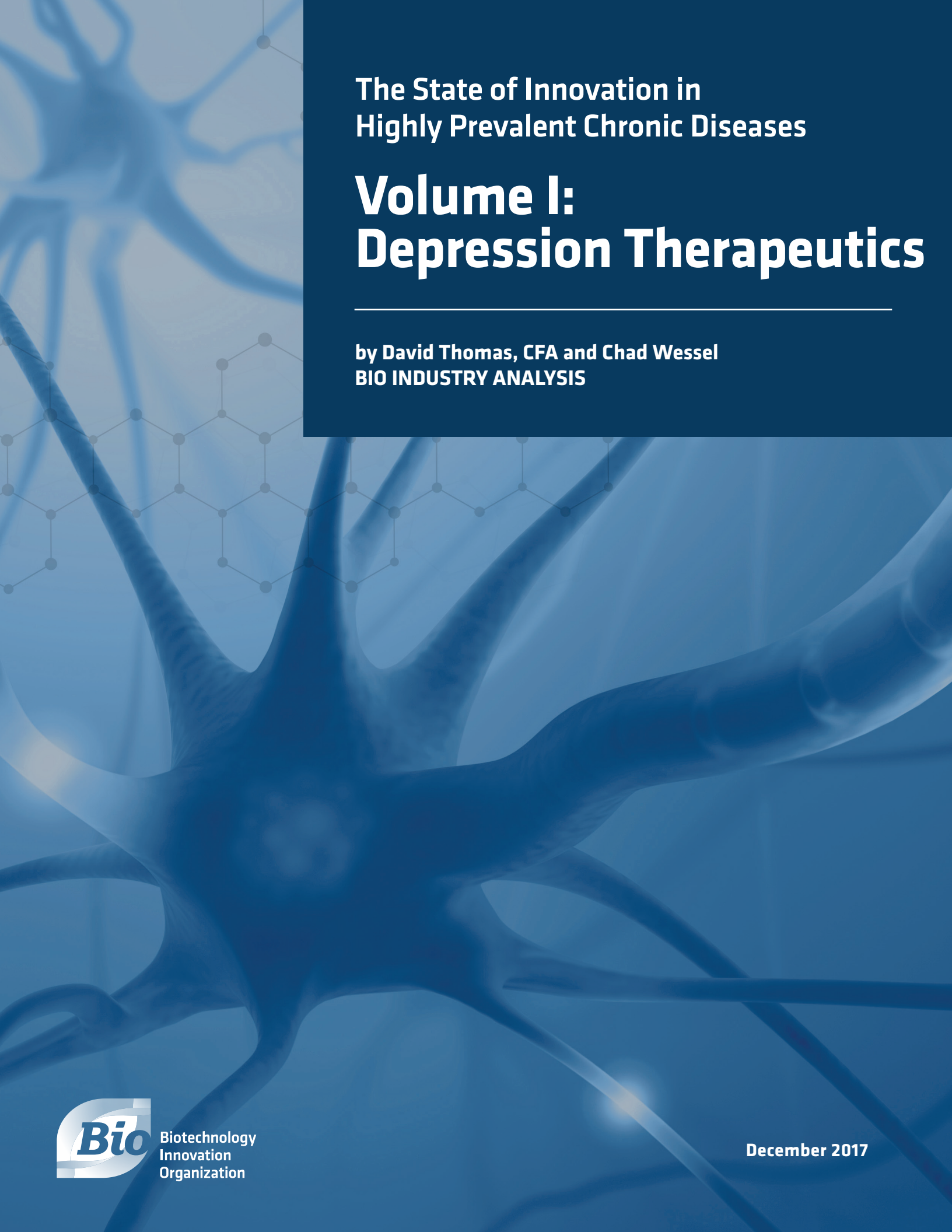

The State of Innovation in Highly Prevalent Chronic Diseases

Volume I: Depression Therapeutics

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BIO INDUSTRY ANALYSIS

Biotechnology Innovation Organization

December 2017

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Introduction

The following report is the first in a series on the current funding and R&D landscape of highly prevalent, chronic diseases. In our previously published research, emerging company investment for drug development in psychiatric disorders, endocrine, cardiovascular, and respiratory diseases was shown to be declining over the last decade and low relative to the prevalence and cost of these diseases (**Figure 1**).[1]

The persistence of this trend could have implications for the future output of innovative medicines in these disease areas. The cause for concern is magnified by the impact these chronic disease areas are having on the overall healthcare system in the US. Thus, it is important that barriers to therapeutic innovation are identified and removed.

We are initiating this series of reports with an in depth look at the state of innovation in depression therapeutics. Depression is the most prevalent psychiatric disorder, with 16 million patients affected in the US alone.[2] Direct healthcare cost for depression in the US has been estimated to be $105 billion.[3]

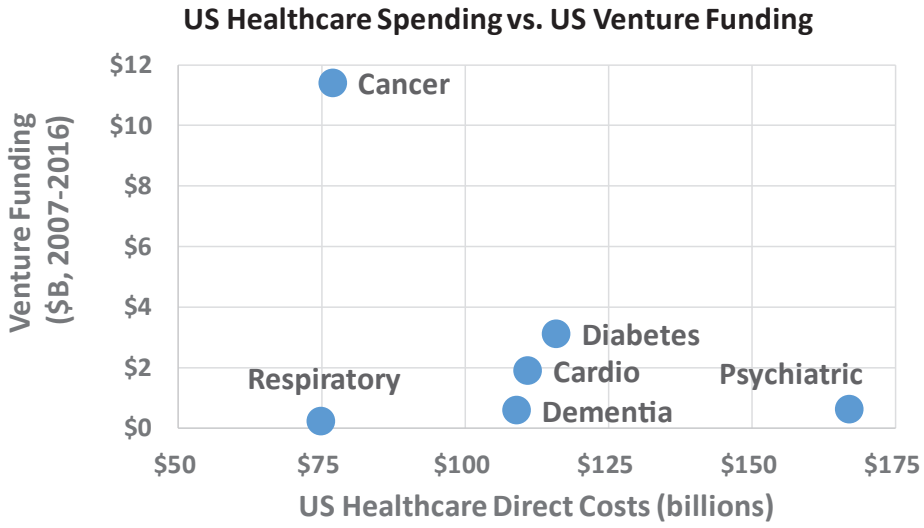
Herein, we analyze all FDA approved drugs and the current clinical pipeline in depression to assess the depth and breadth of innovation. Historical clinical success rates and failed mechanistic strategies are also identified. Lastly, we examine the last decade of venture investment as well as clinical trial initiations.

Key Takeaways

- There is a significant unmet need for new therapies for the treatment of depression. Only 29 active substances have been approved for major depression since 1959, and work on a single hypothesis.
- Promising new therapeutic approaches, based on unique molecular targets discovered in the 1990s and early 2000s, have experienced a significant number of setbacks. Currently, there are now only 33 drug programs in clinical trials utilizing new approaches for major depression.
- Clinical trial initiations for new therapeutics are down 50% over the last decade, and drug candidates for new clinical studies are nearly non-existent.
- Venture investment in companies focused on depression is at record low levels.

[1] Thomas, D., Wessel, C. BIO Industry Analysis. Emerging Company Trend Report, (2017) (www.bio.org/iareports)
[2] NIMH (2015): https://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml
[3] J. of Clinical Psychiatry, v76, (2):155–162 (2015)

DISEASE PREVALENCE AND HEALTHCARE COST VS. VENTURE CAPITAL FUNDING FOR HIGHLY PREVALENT CHRONIC DISEASES



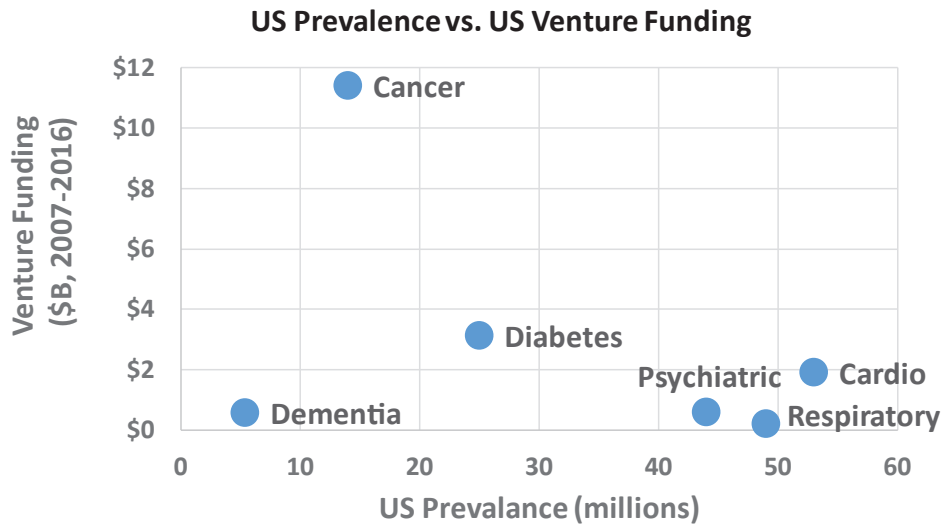


Figure 1. Prevalence and Cost vs. Venture Capital Funding 2007-2016 for Oncology, Psychiatry and other highly prevalent, chronic diseases. [Source for prevalence: Cardiovascular: 2015 data from Circulation, Heart Disease and Stroke Statistics – 2016 update (2015); Psychiatric Disorders: 2010 data from NAMI for "Mental Illness", Respiratory: unknown; Endocrine: 2007 data compiled by CDC; Cancer: 2014 data from SEER. Source for healthcare cost: Health Affairs, 35, No. 6 (2016). Source of venture data: BIO Industry Analysis, Emerging Company Trend Report, 2017.]

Historical Perspective of Depression Therapeutics

Depression is broadly defined as a mood disorder associated with feelings of sadness and loss of interests, with multiple symptoms potentially accompanying an overall change in daily functioning including insomnia/hypersomnia, weight loss/gain, fatigue, excessive guilt, and suicidal ideation.[4] The most prevalent form of depression is unipolar depression, or major depressive disorder (MDD). Depression also persists in other mental health disorders such as bipolar disorder, postpartum depression, and seasonal affective disorder (SAD). Although there is some overlap, treatments for unipolar and bipolar depression are not the same. We focus here on the most prevalent unipolar form of depression, MDD.

FDA Approved Medicines for MDD

All FDA approved drugs for MDD fall into a single strategy or hypothesis – modulation of the brain's monoamine neurotransmitter levels. For example, many drugs elevate the levels of brain serotonin, a major monoamine neurotransmitter that has a role in regulating mood levels such as happiness, anxiety, and social behavior.

Although current therapeutic interventions work by modulating monoamine levels, the mechanistic routes to achieve this are varied and have been refined over the last six decades. Most of these refinements have led to better safety and side effect profiles. Even with these advances, there remains a large unmet need in the field of depression. For example, the issue of delayed onset of benefit, often well over a month with current therapies, remains an issue. About half of the patients who receive a benefit do not respond to the first medicine prescribed and must journey through months of trial and error to find the right drug. Further, a third of patients never realize any benefit from monoamine modulating therapies.[5]

Analyzing the EvaluatePharma database of 218 FDA approvals for MDD, we found that only 29 unique active substances have been approved since 1959 (when the first monoamine modulating drug, imipramine, was approved).[6,7] (See **Appendix 1** for a list of all 29 compounds listed by year of FDA approval). Of the 218 FDA approvals, 157 were generic approvals and 51 were New Molecular Entity (NME) approvals. A closer look at these NMEs reveals a mix of unique molecules, extended release and new drug delivery formulations. These advances in delivery technologies have been beneficial to patients in that they improved safety and compliance. Some of the earliest drugs had a long list of side effects and ran the risk of overdose, making dosing and compliance difficult to manage. Newer drugs overcame some of these obstacles, but efficacy remained at similar levels through the decades.

Because of the long history of development of monoamine modulating drugs and their reformulations, most of the currently marketed drugs that target this pathway are now generic (**Figure 2**).

[4] https://www.psychiatry.org/patients-families/depression/what-is-depression (accessed September 2017)
[5] NIMH Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study, https://www.nimh.nih.gov/funding/clinical-research/practical/stard/allmedicationlevels.shtml
[6] EvaluatePharma database (www.evaluategroup.com) accessed July 2017
[7] Lopez-Munoz, F. et al. Monoamine Neurotransmission: The history of Antidperessants from 1950s Until Today. Curr. Pharm. Design, 15, p1563-1586 (2009)

ORIGINAL FDA APPROVALS FOR DEPRESSION 1959-2016
NOVEL ACTIVE INGREDIENTS ONLY

		Tricyclics and MOAs	Tetracyclics and Wellbutrin	Prozac era (SSRI, SNRIs)	Next Gen Specificity	
Class I (Strategy)	Class II (primary target category)	1959-1969	1970-1986	1987-2006	2007-2016	Total
Monoamine modulation	SER, NOR transporters	5	1	2	0	8
Monoamine modulation	MAO	3	0	1	0	4
Monoamine modulation	SER NOR receptors and transporters	0	1	1	0	2
Monoamine modulation	NOR transporters	0	1	0	0	1
Monoamine modulation	SER, NOR, DOP transporters	0	1	0	0	1
Monoamine modulation	SER receptors	0	1	0	0	1
Monoamine modulation	SER transporters	0	1	5	0	6
Monoamine modulation	SER, NOR receptors	0	0	1	0	1
Monoamine modulation	SER receptors and transporters	0	0	0	2	2
Monoamine modulation	SER, DOP, NOR receptors	0	0	0	3	3
Total		8	6	10	5	29

Figure 2. All FDA approved active ingredients for Major Depression since 1959, categorized by strategy and primary molecular target. (Note that iproniazid, an MOA inhibitor, was approved for tuberculosis in the 1950s and used off label for depression. It was later withdrawn due to liver toxicity. Amphetamine had been used for depression prior to the 1938 U.S. Food, Drug, and Cosmetic Act.) Abbreviations: MAO, Monoamine Oxidase; SER, Serotonin; NOR, Norepinephrine; DOP, Dopamine. Source: BIO Industry Analysis, EvaluatePharma, Biomedtracker, fda.gov, company websites, Wikipedia, 2017.

A deeper dive into the mechanism of action of the 29 active ingredients approved since 1959, reveals that change in specificity for monoamine targets (monoamine transporters, receptors, or metabolizing enzymes) has been the primary innovation of the industry's R&D efforts. Reflecting on these last six decades of drug R&D in pursuit of better monoamine modulators, we see four distinct periods of innovation. The first period, expanding throughout the 1960s, opened the door for modern psychopharmacology with the discovery and eventual FDA approvals of the TriCylic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs). Although the exact targeting was not known at the time, most of the TCAs developed were later found to boost levels of serotonin and norepinephrine mainly by interacting with transporter proteins in brain cells. Meanwhile, MAOIs acted to prevent monoamine breakdown, thereby increasing its concentration in neuronal synapses.

The 1970s and 1980s saw the second period of innovation with the emergence of the tetracyclic class of antidepressants, as well as drugs that targeted another monoamine, dopamine, in addition to serotonin and norepinephrine. A well-known example of a more dopamine sensitive drug was the introduction of Wellbutrin (bupropion) in 1985.

The third period, and perhaps the most significant period for depression drug development, was the approval of the first Selective Serotonin Reuptake Inhibitor (SSRI), Prozac, in 1986. The discovery and eventual FDA approval of Prozac highlights the continued efforts in the 1980s to make drugs more and more specific to individual monoamine transport proteins. These SSRIs were quickly followed by Selective Norepinephrine Reuptake Inhibitors (SNRIs) that were selective for norepinephrine transport proteins found in brain cells.

The fourth, and most recent phase, is defined by more specific targeting of the monoamine receptors, either alone or in addition to transport systems. As molecular pharmacology advanced in the 1990s, more receptor types were discovered allowing for improved biochemical specificity to be engineered for a particular monoamine. Serotonin, for example, was found to have 14 receptor subtypes by the mid 1990s, half of which have now been targeted by drug developers.[8]

[8] Malenka, R. et al. Molecular Neuropharmacology: A Foundation for Clinical Neuroscience. Ch.1, p3-16 (2009)

Efforts to Innovate Beyond Monoamines

As a recent cover article in Time magazine highlighted, many psychiatrists are looking for new medicines in this field. Dr. Roy Perlis, director of the Center for Experimental Drugs and Diagnostics at Massachusetts General Hospital, told Time in a recent interview "We have no idea, after many decades of studying these drugs, why some people get better and some people don't", "We desperately need truly new interventions."[9]

Looking at depression R&D outside of monoamine targeting, we see a notable attempt by industry to pursue new strategies proposed in the late 1990s and early 2000s. Much of the new strategies were the result of basic molecular biology research in the areas of neuroendocrinology, neuroinflammation, and neuroplasticity. However, many of these new strategies have been unsuccessful, with some completely abandoned, and others revamped with second or third generation compounds (Figure 3). Examples of what was promising just 10 years ago include drugs targeting neurokinin, muscarinic acetylcholine, and Corticortopin Releasing Factor (CRF) receptors. These were widely accepted as the most promising targets for future depression drugs.[10] Each of these, and numerous other target categories, have fallen short in proof-of-concept human studies or in larger registration enabling trials.

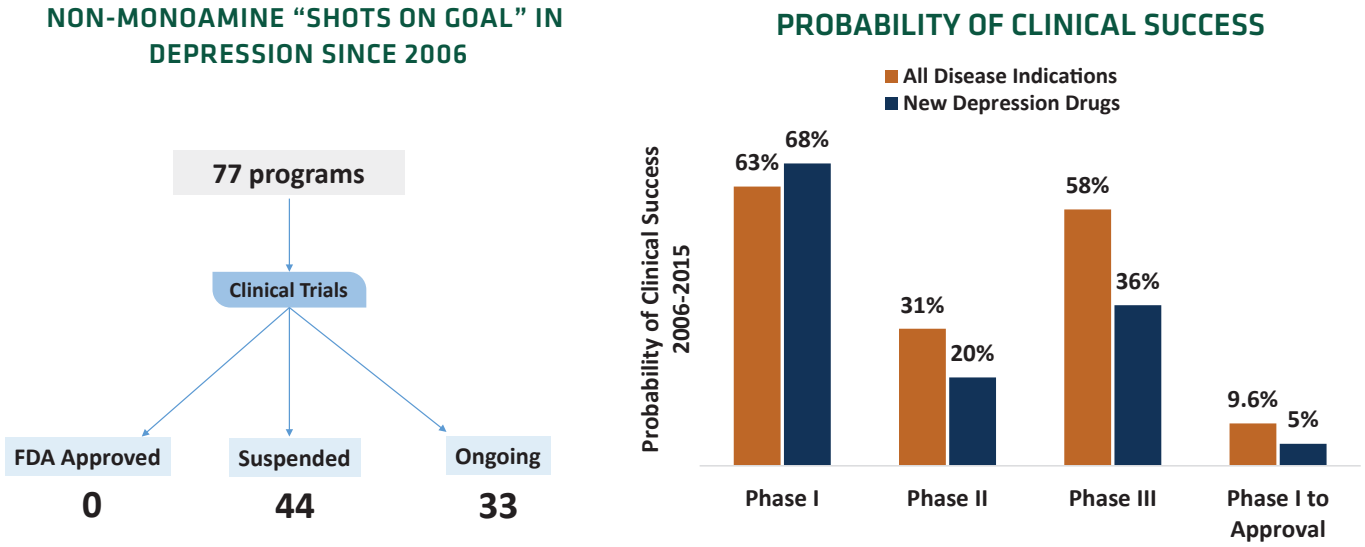


Figure 3. Left: Non-monoamine programs that have been under way since 2006, and the number officially suspended vs. ongoing as of October 2017. Right: Clinical success rates for MDD, compared to overall industryprobabilities based on approximately 10,000 drug programs run from 2006-2015. The MDD programs analyzed for success rate calculations include novel monoamine modulating drugs.

Analyzing the R&D programs that were active in the period 2006-2017, we found that of 77 clinical programs targeting new targets (non-monoamine based), 44 are now suspended while 33 are ongoing. This significantly high number of failed programs has contributed to low clinical success rates seen in recent studies of psychiatric drug development overall.

The broader psychiatric drug development disease area was found to have the highest failure rate for Phase I and Phase II clinical trials of any major disease category in our most recent study of clinical success rates.[11] For example, psychiatric drug development programs in Phase II had only a 23.7% chance of success of transitioning to Phase III, and a 56% chance of transitioning from Phase III to NDA filing..

When looking at new molecular entities in MDD specifically, a similarly poor record was found with 36 of 45 Phase II programs, and 7 of 11 Phase IIIs suspended. These high Phase II/III failure rates in depression were a major contributor to the low overall probability of success of 5.0% for drug programs moving from Phase I through FDA approval compared to 9.6% across all disease areas. This may be indicative of the challenges in translating positive preclinical data for drug candidate into safe, efficacious psychiatric medicines.

[9] Oaklander, M. New Hope for Depression. (May 2017) http://time.com/4876098/new-hope-for-depression
[10] Rupniak, N. Curr Opin Investig Drugs. 2002 Feb;3(2):257-61.
[11] Thomas, D., et al. BIO, BioMedtracker, Amplion. Clinical Development Success Rates 2006-2015 (2016) (Accessed at www.bio.org/iareports)

Current Clinical Pipeline in MDD

With only 33 ongoing clinical programs and a historically low probability of success, there is a lack of breadth and depth in today's MDD pipeline. In contrast, consider the highly differentiated oncology pipeline with 1,319 investigational compounds across 2,385 active clinical programs.[12] Oncology's sub indications, such as breast cancer, lung cancer, and leukemia, have more than 125 programs each – four times the amount found in MDD. Depression drug candidates represent only 0.2% of the global drug pipeline, not a balanced allocation considering there are 16 million people with depression in the US alone.[13]

Grouping the current clinical programs in MDD into the therapeutic target strategies reveals only nine strategies outside the monoamine strategy. Most strategies do not have multiple compounds in Phase II/III trials, making for a statistically low probability of success.

One exception to this is the most represented strategy, modulation of the glutamate system. Multiple receptors that bind glutamate have been shown to be potential targets for depression. Almost one third of the drug candidates in development target the glutamate system, while others may have indirect or secondary effects on glutamate neurotransmission.

Beyond the glutamate targets[14], there is a mix of inflammatory, endocrine, and neuropeptide targets under investigation in drug intervention studies for depression. The five Phase III candidates listed in **Figure 4**, are each quite unique and utilize different molecular mechanistic approaches to achieve clinical benefit in depression. As these offer the earliest chance of market entry, we have expanded on each in **Appendix 2**.

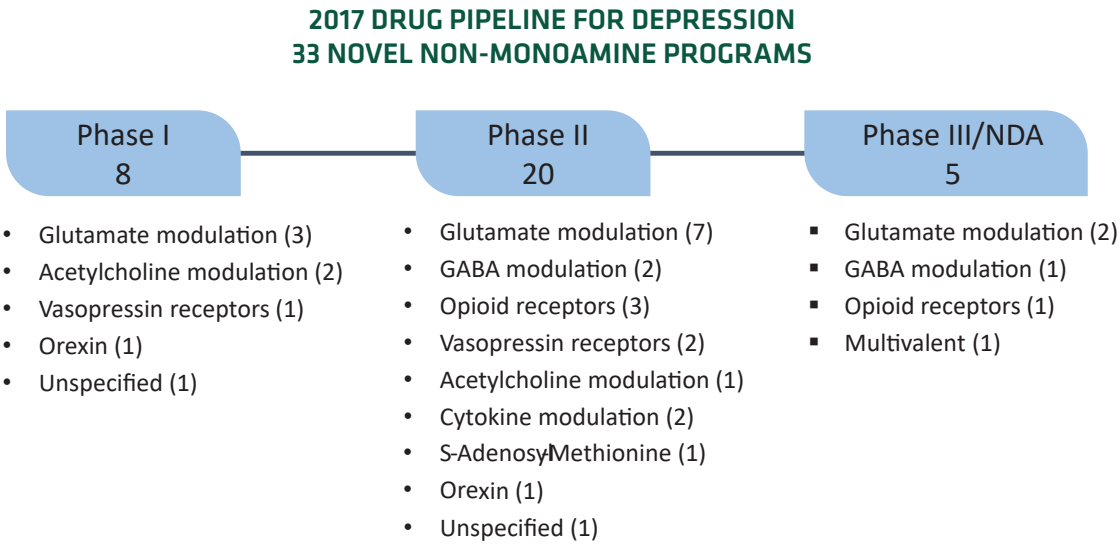


Figure 4 The currently active pipeline, based on Biomedtracker's methodology*. The drug targeting strategy listed is based on the primary target of the novel compound under development. For combination drugs, only the novel active component's target is listed.

To predict what may enter the clinical pipeline in the near future, we looked at all listed preclinical depression programs in the Biomedtracker and EvaluatePharma databases. Only four of the 11 preclinical programs found had drugs for unique targets not currently in the clinic or previously approved.[15] Such a low number of candidates is further suggestive of a weakening early stage pipeline.

Other developments in the field of depression, mainly outside the traditional drug development path, surround the perturbation of brain networks and/or the interconnections of these networks. For more on these developments, see **Appendix 3**.

[12] Data for oncology R&D pipeline is taken from the BioMedTracker database, and current as of April, 2017.)
[13] Only 33 drugs of 5,956 total programs BioMedTracker database in 2017.
[14] The most vetted glutamate targets in drug development are the two well-characterized receptor types, NMDA (N-Methyl-D-Aspartate) receptors and AMPA (α-Amino-3-hydroxy-5-Methyl-4-isoxazolePropionic Acid) receptors. There are two other receptor types, metabotropic receptors, which are targeted in two Phase I programs, and the less understood kainic acid receptors. It should be noted that the glutamate system is related to the GABA (γ-Aminobutyric acid) system, also prevalent in the clinical pipeline shown in Figure 4. Glutamate is a precursor for the synthesis of GABA.
[15] Novel targets found with active preclinical programs: COMT, TCAP-1, MAP-2, and PKC

Trends in Venture Investment and Clinical Trial Initiations

Uncovering the exact dollar amounts that private and public companies are spending on depression drug development has limitations. Nevertheless, we have outlined below a few methods of approximating the level of private company investment and the broader industry R&D activity. For small companies, we can identify companies with lead compounds in depression and assess venture funding over time. More broadly, we look at the total industry R&D pipeline to determine the level of support for new depression drug candidates.

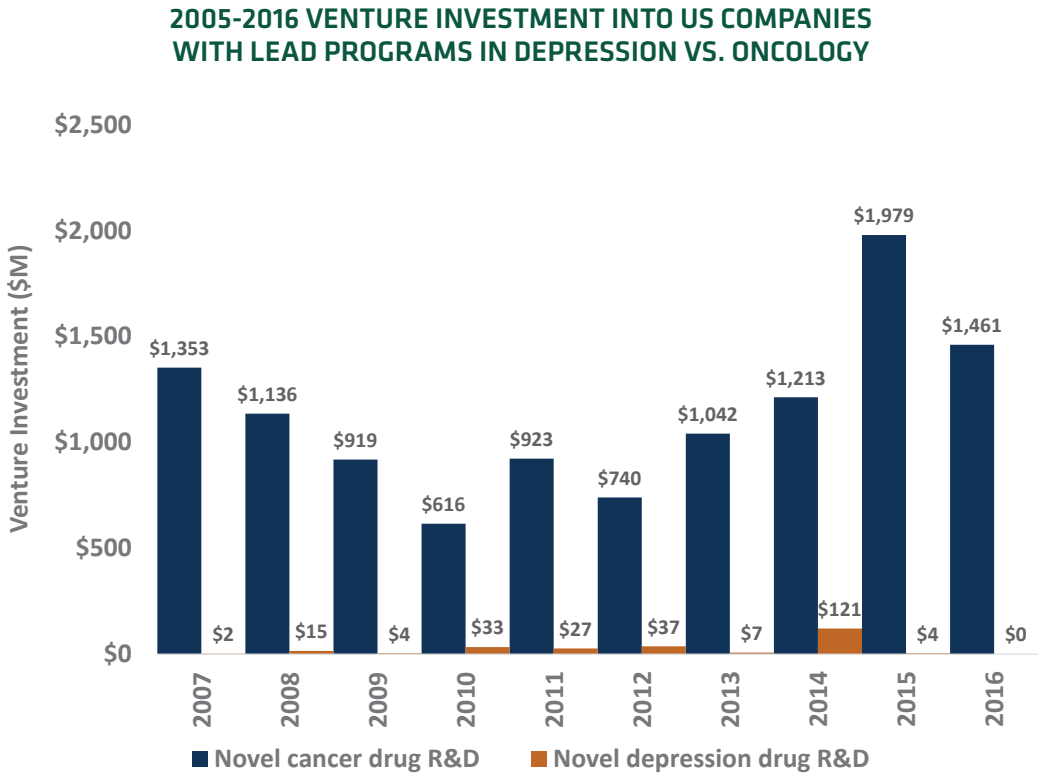


Figure 5. Venture funding of companies with lead products in depression vs. oncology, 2005-2016. For depression, only one or two companies per year receive funding.

Venture investment into US companies with lead depression products is essentially at a standstill. Using the "lead product" method for tracking venture investment, there were only two companies meeting this profile in 2015 and none for 2016. During the same period, there were a total of 657 companies financed across a range of therapeutic companies. US oncology companies, by comparison, received $3.44 billion across 173 companies over the last two years. Even when we include funding of companies in all psychiatric indications as their lead products, the level of funding is 10-fold less than oncology. The broader "psychiatric disorder" category (all companies developing a lead product for *any* psychiatric disease) received only $291M across 24 companies. This suggests investors currently lack conviction to support new approaches in depression as well as other psychiatric indications.

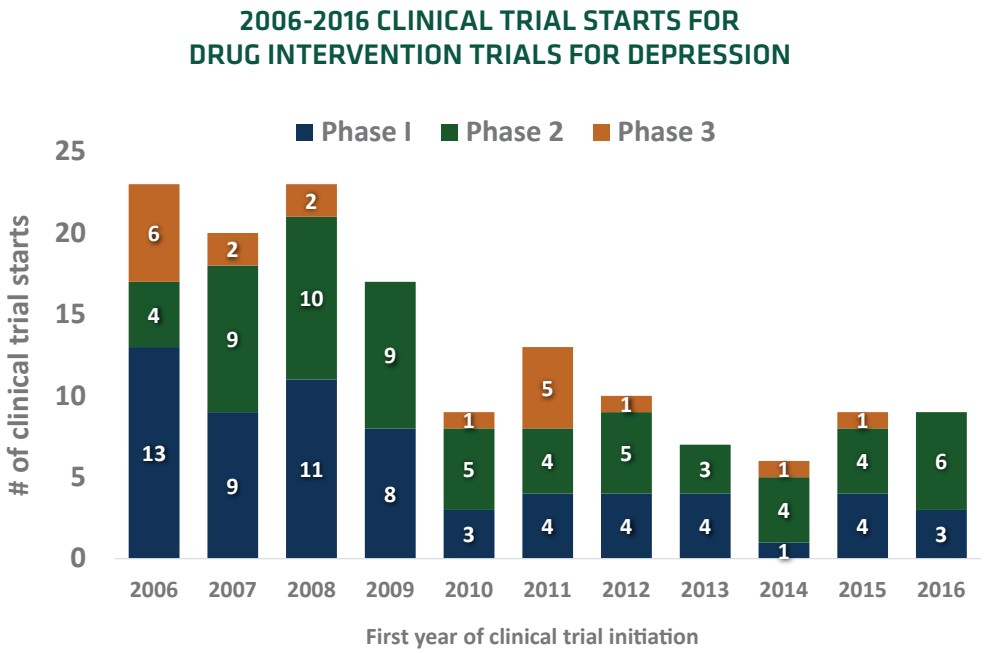


Figure 6. Clinical trial starts for MDD, 2006-2016. TrialTrove data accessed May 2017. A total of 697 clinical trial starts were retrieved from TrialTrove (on May 2017) and individually assessed for novelty of drug (no prior approval history of the active compound) and trial phase cohorts de-duplicated. A total of 146 novel drug intervention trials were initiated during the period 2006-2016.

Looking at clinical development programs, where substantial R&D costs are incurred, we found clinical trial initiations have been trending down over the last decade. Based on an analysis of TrialTrove data, novel drug intervention trial starts are down 50% in the recent five-year period (2012-2016, n=82) compared to the prior five year period (2007-2011, n=41). Phase I clinical trial starts dropped more than 50% over this period, suggesting a slowing of new candidates coming out of basic research and preclinical development. Phase II trial starts declined by 40%, and only two Phase III trials for novel depression drugs were initiated in the last five years.

Although our original observations surrounded the drop in small company investment, the clinical trial initiation data suggests the problem of slowing R&D for depression drug development extends to public companies as well. As R&D costs are most concentrated in Phase II and III trial costs, the lack of new trial starts suggests depression drug R&D spending across the industry is down significantly.

Challenges to Innovation

Impediments to innovative drug development fall into three broad areas: scientific, regulatory, and commercial.

Scientific challenges. Scientific hurdles to successful drug development for depression include a lack of predictive animal models, difficulty delivering and assessing pharmacokinetic profiles in the brain, a low number of targets, and high heterogeneity in the patient population.

Reliable animal models that can provide predictive signals of translational efficacy remain a significant needed tool in the discovery repertoire of depression research. Certain properties of the human brain, such as the blood brain barrier, have prevented predictive preclinical model development. Such properties have also limited the application of many new biologic technologies. When we look at the diversity of modalities in the depression pipeline, not a single example of gene and cell therapy exists, and only a single biologic can be found (one antibody in Phase II). Future progress will likely continue to rely on the skills of medicinal chemists, delivery methods, and the discovery of new molecular targets. This contrasts with many other disease areas where advances in biologic modalities are changing the face of medicine.

Heterogeneity in the MDD patient population makes it difficult for precise drug targeting, an advantage that areas like oncology and rare metabolic disorders have benefited from. Within oncology, many of the 80+ indications now have known genetic mutations that profile tumor types. This is allowing companies to develop drugs targeted to a specific patient population as they initiate clinical trials. On the other end of the development spectrum, depression clinical researchers do not yet have reliable biomarkers, or other methods, for patient stratification.

Regulatory challenges. In addition to large Phase III efficacy trials, which can require enrolling thousands of patients in a single study, drug developers in MDD may be required to run large cardiovascular safety outcome studies due to the large disease population. The large trial size makes such trials expensive, some reaching hundreds of millions of dollars, making it highly burdensome for small companies. This contrasts with oncology and rare disease trials where substantially fewer patients are enrolled in registration enabling studies.

Commercial challenges. The current market landscape for depression drugs may also be impacting R&D incentive. Over 90% of the prescribed medicines for depression are generic. For a new innovative drug to recoup investment with expected risk-adjusted returns, it must be far superior to those on the market. However, investors have learned in recent years from drug launches in other chronic, highly prevalent indications, that even with highly innovative drugs the reimbursement challenges can be so great that return on investment is uncertain. In light of these recent examples, management and investors have become more cognizant that the reimbursement landscape has changed, and portfolios are being managed with this in mind.

Summary and Discussion

Recent R&D trends, investment levels, and depth of the current clinical pipeline analyzed in this study reveal a cause for concern for future innovation in depression therapeutics. Clinical trial initiations were found to have dropped 50% in recent years for novel drug candidates in depression, and only three Phase III trials were initiated in the last five years. Venture investment into companies with lead programs in depression was found to be virtually non-existent over the last few years. This contrasts with near record levels of investment, over $5 billion annually in recent years, in other therapeutic areas. The clinical pipeline for new approaches to treat depression consists of just 33 novel drug candidates, with only five in Phase III testing. Although nine separate approaches were found among these candidates, only one approach (glutamate modulation) was found to have breadth in terms of number of differentiated programs.

The limitations of currently marketed depression drugs, which were found to target a single biological hypothesis, suggest more therapeutic options are needed to address patient's needs. The data described above point to a potential shortfall in meeting this unmet need. Solutions are needed today for companies and investors to make innovation in depression a priority. We urge policymakers and the industry to think creatively about how trends observed in this analysis can be reversed.

Treatment of depression presents a monumental challenge as our basic understanding of brain biology is limited. Looking back decades ago, cancer was also a poorly understood and monolithic disease, with only limited, toxic chemotherapies available. Today we view cancer as more than 80 distinct indications, each with many subsets correlated to DNA mutations. Cancer drugs are highly differentiated and target by tissue/indication type and increasingly for mutation type. For depression drugs to succeed in the clinic, the subsets of different types of depression and the biological basis of each disease will need to be better understood. There is now mounting evidence that for some versions of depression, an inherited genetic basis exists.[16] As precedents are set elsewhere in precision medicine, future drug targeting strategies for depression may benefit by incorporating trial enrollment strategies based on genetic variation to select the right patients for the most appropriate treatment.

A complementary step to building a path forward in advancing our understanding of the brain should include continued government funding of basic research. Numerous projects that have been initiated in the last decade to map the complex circuitry of the 100 trillion connections inside the brain. In the US, the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative supports brain mapping as part of its long-term goals. The 21st Century Cures bill, signed by President Obama in late 2016, added $1.5 billion in funding to this program over the next 10 years.[17,18] This research funding will bring together advances in neural imaging to help our understanding of brain disease etiology. This may eventually bring about better methods for preclinical assessment of drug candidates, early clinical surrogate brain signatures and biomarkers.

Other beneficial programs are also underway that will complement this basic research on the brain. Patient registries will eventually serve as an important resource for psychiatrists to better understand mental health conditions and develop new treatments that improve outcomes and functioning of patients. For example, the National Network of Depression Centers is collaborating to expand the mental health registry maintained by the American Psychiatric Association.[19] The development of standards for patient reported outcomes will also be helpful to better understand patient response to therapy and self-assessed benefit-risk profiles. Mobile technology should also be embraced as it will likely play a critical role in this interaction, in addition to its potential role in diagnosing mental states.

[16] Niciu, M. et al. Biomarkers in mood disorder research. Arch Clin Psychiatry, 41 (5), p131-4 (2014)
[17] Hudson, K., Collins, F. New England Journal of Medicine, 376, p111-113 (2017).
[18] https://www.braininitiative.nih.gov/
[19] https://www.psychiatry.org/newsroom/news-releases/national-network-of-depression-centers-to-collaborate-on-psychpro-apas-mental-health-registry

Appendix 1 – Active compounds of FDA Approved drugs for Depression

Below is a list of each active compound and year of first FDA approval. Excludes later versions with new formulations and stereoisomer isolates. Source: BIO Industry Analysis, EvaluatePharma, Biomedtracker, fda.gov, company websites, Wikipedia, 2017.

29 NOVEL ACTIVE COMPOUNDS 1959-2016*
FDA APPROVAL DATE AND PATENT STATUS

	Active Ingredient	FDA Approval	Brand
1	imipramine	1959	Tofranil
2	isocarboxazid	1959	Marplan
3	amitriptyline	1961	Elavil
4	phenelzine	1961	Nardil
5	tranylcypromine	1961	Parnate
6	desipramine	1964	Norpramin
7	protriptyline	1967	Vivactil
8	doxepin	1969	Sinequan
9	nortriptyline	1977	Pamelor
10	amoxapine	1980	Asendin
11	maprotiline	1980	Ludiomil
12	trazodone	1982	Oleptro
13	trimipramine	1982	Surmontil
14	bupropion	1985	Wellbutrin
15	fluoxetine	1987	Prozac
16	sertraline	1991	Zoloft
17	paroxetine	1992	Pexeva
18	venlafaxine	1993	Effexor
19	nefazodone	1994	Serzone
20	mirtazapine	1996	Remeron
21	citalopram	1998	Celexa
22	escitalopram	2002	Lexapro
23	duloxetine	2004	Cymbalta
24	selegiline	2006	Emsam
25	aripiprazole	2007	Abilify
26	quetiapine	2009	Seroquel
27	vilazodone	2011	Viibryd
28	vortioxetine	2013	Trintellix
29	brexpiprazole	2015	Rexulti

Generic

On Patent

*excludes Extended Release and other formulations and enantiomer isolations

Appendix 2 – Phase III drug programs.

The five current Phase III drugs in development for depression are listed below:

1. **Rapastinel** (Allergan). Rapastinel, is a novel small peptide that activates the glutamate receptor.[20]

2. **Esketamine** (JNJ). Esketamine, an enriched enantiomer of ketamine, targets the glutamate system, as well as a few other targets in the brain such as the sigma-1-receptor and opioid receptors. [21]

3. **Brexanolone** (Sage Therapeutics). Brexanolone, or Allopregnanolone, is a neurosteroid that targets the GABA-A receptor, the same receptor benzodiazepines act on.[3]

4. **ALKS 5461** (Alkermes). ALKS 5461 consists of two drugs targeting two different opioid receptors. One of the two active compounds is buprenorphine, a previously approved drug that targets both opioid receptor kappa and mu. The other component is samidorphan, which blocks opioid receptor mu activity. ALKS 5461 is currently in the process of NDA submission. (Buprenorphine blocks the activity of the kappa receptor, but boosts the activity of the mu receptor. Samidorphan blocks opioid receptor mu activity nulling the addictive characteristics of buprenorphine.)

5. **AXS-05** (Axsome). AXS-05 is a novel, oral, investigational drug product that utilizes Axsome's technology of combining bupropion and dextromethorphan. (Dextromethorphan has multiple targets, including the sigma-1 receptor and monoamine reuptake. Bupropion, is a previously approved norepinephrine and dopamine reuptake inhibitor with some nicotinic acetylcholine receptor activity.) [22]

Appendix 3 – Innovations outside the traditional drug development path

Modern neuroscience, through advanced imaging techniques, has shown a relationship between poor mental health and disturbances of normally functioning neural circuitry.[23] Current clinical work to probe the efficacy of drugs that modulate these brain networks are underway. Below are some of these interventions that are likely acting on multiple networks or pathways:

- **Hallucinogens.** Serotonergic hallucinogens have been tested recently on depressed patients under strict medical supervision and guidance, findings thus far have yielded positive outcomes.[24,25]

- **Deep Brain Stimulation (DBS).** For DBS, a small electrical stimulating device is implanted in the brain and used to "reset" disturbances in neural networks of drug-resistant depressed patients.[26] Unfortunately, the first clinical study of DBS targeting one area of the brain has not shown statistical benefit.[27]

- **Repetitive Transcranial Magnetic Stimulation (rTMS).** Magnets have also been shown to improve signs of depression. In 2008, the FDA approved Repetitive Transcranial Magnetic Stimulation (rTMS) as a treatment to alleviate symptoms of mildly treatment-resistant depression. As with **ElectroConvulsive Therapy (ECT),** this is offered to patients that do not respond to drug therapy and classical psychotherapy (such as **Cognitive Behavior Therapy, CBT**).[28]

[20] The biochemical mechanism is very different from other NMDA glutamate receptor drugs. Rapastinel is a tetrapeptide allosteric partial agonist that does not bind to the intrinsic glycine site of the NMDA receptor complex. Biomedtracker.
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Appendix 4 – Suspended Programs

APPENDIX 4A - ABANDONED TARGET STRATEGIES SINCE 2006

Anandoned Target Category	Most Advanced Phase
Glucocorticoid receptors	Phase III
Neurokinin receptors (e.g. Substance P)	Phase III
Muscarinic acetylcholine receptor	Phase III
Corticotropin Releasing Factor Receptor 1	Phase II
Opioid receptor Delta	Phase II
Fatty Acid Amide Hydrolase	Phase II
N-Acetylated-Alpha-Linked-Acid-Dipeptidase	Phase II
P38 kinase	Phase II
Omega-3	Phase II
Multivalent approaches (multidomain molecules):	
NMDA Glu receptors + SER transporters	Phase III
Sigma-1 receptor + SER NOR transporters	Phase II

APPENDIX 4B - SUSPENDED PROGRAMS BY TARGET, SINCE 2006

		Suspended Program Phase			
Target Category	Strategy	Phase I	Phase II	Phase III	Total
NMDA Glu receptors	Glutamate modulation	5	2	0	7
CRF receptors	CRF modulation	2	4	0	6
Metabotropic Glu receptors	Glutamate modulation	0	4	0	4
Neurokinin receptors	Tachykinin modulation	0	3	1	4
nACH receptors	Acetylcholine modulation	0	2	1	3
mACH receptors	Acetylcholine modulation	1	1	0	2
Glucocorticoid receptor	Glucocorticoid modulation	0	1	1	2
AMPA Glu receptors	Glutamate modulation	0	2	0	2
FAAH	lipid modulation	0	2	0	2
ORdelta	Opioid receptors	0	2	0	2
Choline uptake	Acetylcholine modulation	0	1	0	1
p38	Cytokine modulation	0	1	0	1
GABA receptors	GABA modulation	0	1	0	1
NMDA Glu receptors + SER transporters	Multivalent	0	1	0	1
NAALADase	Glutamate modulation	0	1	0	1
Omega-3	lipid modulation	0	1	0	1
Melatonin receptors	Melatonin modulation	0	0	1	1
Sigma-1 receptor	Sigma receptor modulation	0	1	0	1
Vasopressin receptors	Vasopressin	0	1	0	1

4a: A list of target categories that were promising a decade ago but are no longer in clinic development in 2017. 4b: A list of targets with number of suspended programs 2006-2017. (Note that for 4b, some target categories listed have active programs, while 4a contains only targets that have been completely abandoned by industry.)

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Acknowledgements

We would like to acknowledge BIO's staff from the Emerging Companies Section (Charles Crain, John Guy, Sesquile Ramon, Danielle Friend) for their review and contributions to this report.