Incentivizing Drug Development for Serious Mental Illness

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Serious mental illness imposes a significant burden on individuals and society. Individuals living with serious mental illness have worse expected health, education, and career outcomes. And while treatments do exist, pharmaceutical innovation in this area has lagged behind many other disease areas, and there is an important need for new treatments. This report describes barriers that have limited innovation in developing new drugs for serious mental illness, including science, research, regulatory, and health system barriers, and presents policies that may incentivize investment in this area.

Burden of Serious Mental Illness in the US

In 2020, approximately 6% of adults in the US (1 in 20 adults) reported living with a serious mental illness.[1] Serious mental illnesses are defined as mental, behavioral, or emotional disorders causing serious functional impairment that substantially limits one or more major life activity.[2] The most common are schizophrenia (1% of adults), bipolar disorder (3%), and severe major depressive disorders (6%).[a, 1, 3, 4] The prevalence of serious mental illness has increased among all age groups over the last decade. In 2020, an estimated 10% of young adults aged 18-25 had a serious mental illness, a rate that is higher compared to adults of other ages (6.9% in ages 26-49, 3.4% in ages 50+).[1]

Individuals living with a serious mental illness face a range of potential mental and physical health comorbidities.[5, 6] They are also at higher risk for substance use disorder and suicide.[7-10] As a result, the average life expectancy of someone living with a serious mental illness is 10 years less than someone without.[11] For those diagnosed with a serious mental illness by age 25, the lifetime costs associated with their condition can be as high as $1.85 million.[11] The annual per-person costs associated with serious mental illness are higher than other diseases like cancer and diabetes,[12] due in part to the high indirect costs of illness. Individuals living with a serious mental illness on average have lower educational attainment, and approximately half the lifetime earnings compared to individuals without serious mental illness.[11]

Living with a serious mental illness is also associated with increased risks of poverty, homelessness, and interaction with the criminal justice system. These risks are even higher among those also living with substance use disorder.[13] In 2020, the Department of Housing and Urban Development reported that approximately 20% of homeless individuals in the US were living with

a These illnesses are not mutually exclusive

a serious mental illness.[14] In addition, one study found that approximately one in four individuals diagnosed with bipolar disorder or schizophrenia were involved with the criminal justice system over a two-year period.[15]

Living with a serious mental illness may also impact relationships, as many individuals depend heavily on help from informal caregivers, typically family and friends, due to the debilitating nature of their illness. Over eight million Americans are unpaid informal caregivers to someone living with a mental illness.[16] Informal caregivers of individuals living with a serious mental illness provide, on average, 32 hours of care each week.[16] As a result of their responsibilities, informal caregivers are more likely than non-caregivers to be unemployed or work fewer hours.[17] In 2020 in the US, informal caregiver costs for schizophrenia alone were estimated to total $83.7 billion in unpaid caregiving and $20.8 billion in additional costs, including personal health care costs. Caregivers of individuals living with mental illness report rates of emotional stress (53%) and physical strain (25%) that are higher than other types of caregivers. [16]

Unmet Need in Serious Mental Illness

While beneficial treatments exist for schizophrenia, major depression, and bipolar disorder, it is often a challenge for patients to find an effective and tolerable treatment regimen to manage their specific condition, in part due to the underlying heterogeneity and complex biology underpinning mental health conditions. [18-20] Medications commonly cause unwanted side effects, which are associated with patient non-adherence.[21] Not all patients will achieve an adequate response to treatment, and many continue to live with symptoms of their condition, resulting in continued functional impairment.[22, 23] In any given year, 40% of individuals with schizophrenia, 50% of individuals with bipolar disorder, and 35% of individuals with major depression are untreated. [24-26]

Barriers to Innovation in Serious Mental Illness

Despite high unmet need, the development of novel pharmaceuticals in serious mental illness has lagged behind advancements in other disease areas over the last 30 years. Most new medications that have entered the market have largely benefitted patients through increased tolerability, or alternative routes of administration (e.g., injection instead of pill), compared to earlier generation treatments. While these advancements have provided incremental benefit to certain patients, new treatments that are effective in treating symptoms and improving the wellbeing of patients living with serious mental illness are urgently needed. A number of barriers have contributed to the slow progress in researching and developing new drugs for serious mental illness. In this report we focus on scientific, research, regulatory, and health system barriers.

Scientific and Research Barriers

Science

The complexity of studying the brain and its basic mechanics is a fundamental challenge to identifying new molecular targets for drugs to treat serious mental illness. The lack of biomarkers in mental health research has made clinical trials more difficult to conduct because there is no way to "objectively" diagnose individuals or assess the efficacy of treatments. There are also no adequate animal models to inform molecular target selection and validation, or to test treatment efficacy. [27]

Government research

Therapeutic advances require investment and collaboration from both public and private research entities. The federal government funds most basic science research through intramural and extramural research funding. This research largely focuses on expanding the foundational knowledge of how diseases develop and manifest,

including the preclinical studies that can improve our understanding of the biochemical mechanisms underlying brain functions.

One major barrier to developing new drugs for serious mental illness is the limited funding that is devoted to serious mental illness at the National Institutes of Health (NIH). NIH funding for research focused on serious mental illness is disproportionately low considering the prevalence and significant burden of illness. For example, sexually transmitted diseases (excluding HIV) received a greater amount of NIH funding in 2021 when compared to schizophrenia, $404 versus $266 million respectively, despite schizophrenia having a significantly higher disease burden in the US.

Industry research

Biopharmaceutical companies initiate and fund the majority of clinical research in the US.[28] Clinical research translates findings from basic science research into new drugs candidates that are tested in clinical trials. However, clinical research of serious mental illness has lagged compared to other disease areas, in part due to the limited understanding of brain mechanisms and molecular targets in these conditions. Due to these knowledge gaps, clinical development timelines for drugs used to treat serious mental illness are some of the longest, clinical trial success rates are lower, and regulatory approval is slower than average.

As a result, over time many large pharmaceutical companies have shifted investment away from serious mental illness,[29] in favor of other therapeutic areas with well-defined disease biology, biomarkers, and drug targets. Between 2015 and 2020, the pharmaceutical industry funded 239 clinical trials for new medications for serious mental illness, compared to over 5,264 cancer trials.[30] In the absence of sustained investment from large pharmaceutical companies, many smaller biotechnology and pharmaceutical firms have entered this market space.

Regulatory Barriers

Insufficient market protection

The US regulatory system for biotechnology can also pose barriers to innovation. The US incentivizes pharmaceutical investment with periods of market protection to cover the costs of research and development and to provide a return on investment. The US government awards medical product developers protection against competition through two primary mechanisms: (1) a period of patent protection, and (2) market exclusivity following regulatory approval. However, the existing market protection periods are disadvantageous to pharmaceutical companies in serious mental illness, given the longer research times and ultimately higher costs of developing a drug in this disease area.

Current design of the FDA's accelerated approval program

The accelerated approval program was established at the FDA to speed access to drugs in areas with significant unmet need. However, the program cannot be used for therapeutic areas that do not have established surrogate or intermediate endpoints, including serious mental illness. As a result, accelerated approval has not had an impact on expediting access to new drugs for these conditions.

Health System Factors

Pharmaceutical companies invest in new drug candidates based in part on the expected return on investment (ROI).[31-33] The ROI is the lifetime global revenue earned from a drug, minus the company's overall drug development costs, including post-approval development, marketing, and pharmacovigilance activities. Expected revenue is determined by the expected volume of sales over time, and the net amount that the pharmaceutical company is reimbursed for these sales.

High expected clinical development costs and the potential for low expected revenues, compared to other therapeutic areas, may discourage companies from investing in serious mental illness. In addition, there is a relatively low proportion of patients living with a serious mental illness who obtain treatment compared to other disease areas, and there is lower expected net revenue given the high proportion of treated patients who are insured through Medicaid. Net revenue from drugs reimbursed under Medicaid is generally lower than drugs reimbursed under most other private and public insurers. In 2017, for example, the average net price for top selling drugs in Medicaid was 65% lower than the average net price in Medicare. [34]The relatively large number of patients living with serious mental illness on Medicaid thus potentially limits the revenue companies may expect for new drugs, and may be a disincentive to investment in this space.

Policy Solutions

The following policies may help reduce the scientific, research, regulatory, and health system barriers outlined above, to help incentivize drug development for serious mental illness.

Policy Solutions to Target Scientific and Research Barriers

Increase government research funding of serious mental illness

To improve fundamental scientific knowledge on the brain and its basic mechanics, the level of NIH funding that is devoted to serious mental illness should be increased to be proportionate to the burden of illness. Opportunities to do this include: (1) Increasing funding to the National Institute of Mental Health (NIMH), and (2) supporting funding for the NIH BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, the largest neuroscience project in history, to advanced understanding of disease mechanisms for serious mental illness. There are also opportunities to support proposals to create an Advanced Research Projects Agency for Health (ARPA-H), an independent health agency that would be tasked with driving biomedical breakthroughs, and including a focus on neuroscience and mental health in the program.

Support public-private partnerships

The Accelerating Medicines Partnership (AMP) program is a public-private partnership between the NIH, FDA, and other public and private stakeholders that aims to produce better treatments and diagnostic tools in focused disease areas. The AMP Schizophrenia (AMP SCZ) program is the first AMP initiative focused on a psychiatric disorder. AMP programs for other serious mental illnesses have not been established but should be prioritized given their potential to accelerate the process of identifying promising biological targets for drug development and to improve the likelihood of successful clinical trials. Reducing failures in clinical trials can incentivize more companies to enter this space and bring new innovative drugs to market.

Regulatory Reform

Market Exclusivity Reform

Regulatory reform to extend market exclusivity terms for psychiatric and other central nervous system drugs can help to ensure that as the science advances, companies are incentivized to start and continue investing in the area. This extended exclusivity period could: (1) attach to existing market protection(s) for which the drug is eligible, or (2) supersede other protections. In either case, the market exclusivity period should be sufficiently long enough to account for the high risk associated with drug development in this area. [35]

Adaptive Licensing

Proposed alternatives to the FDA's accelerated approval program include adaptive licensing pathways, which allow for the conditional approval of drugs based on smaller studies of clinical endpoints than those currently conducted for traditional approval. Following the conditional

approval, further studies of the drug would continue and approval could be expanded or rolled-back based on emerging evidence on the drug's efficacy and safety. Using this adaptive licensing pathway could make investments in certain therapeutic areas, including serious mental illness, less risky and thereby encourage greater investment.

FDA Neuroscience Center of Excellence

Proposals to address lengthy regulatory approval periods for central nervous system drugs, including those for serious mental illness, include developing a Neuroscience Center of Excellence (NCOE) at the FDA. The NCOE would consolidate neuroscience expertise within the agency and create processes to expedite the review and approval of potential therapies and diagnostics for these conditions.

Policies to Address Health System Barriers

Increase access to treatment

Compared to other disease areas, the relatively low proportion of patients with serious mental illness who receive treatment could limit expected revenue from drug development in these conditions, and therefore discourage investment. To reduce this barrier, initiatives that improve the mental health care system and increase access to treatment are needed. As one example, the shortage of mental health professionals in the US is a significant problem and barrier to access given the growing prevalence of serious mental illness. Among other reasons, salaries in this field are lagging behind other areas, resulting in relatively fewer mental health care workers in the US. Recent legislative proposals have advocated for increased loan repayment programming for mental health care workers who work in underserved areas. [36] This proposal has the potential to improve access to care for individuals with public insurance options like Medicaid, who make up a significant portion of the serious mental illness patient population.

Insurance

Because a large proportion of patients living with a serious mental illness are covered by Medicaid, the relatively low net reimbursement realized by manufacturers under this program potentially limits expected revenue for new drugs, and may be a disincentive to investment in this space. Policy makers should consider proposals for Medicaid reform that align payment of drugs to treat serious mental illness with economic value. This can better incentivize research and development efforts for therapeutics that provide high value to Medicaid beneficiaries, including medications for serious mental illness.

Conclusion

There is an important need for new treatments for individuals living with a serious mental illness. To incentivize pharmaceutical companies to invest in clinical research in this area, increased government funding for basic science research of the brain should be complemented with public-private partnerships, regulatory reform, and, health system improvements.

Incentivizing Drug Development For Serious Mental Illness

The goal of this report is to summarize the burden of serious mental illness in the US, the need for new therapies, and the importance of both public and private investment in bringing new therapies to market.

To this end, the report describes the history of pharmaceutical innovation to address serious mental illness and barriers to researching and developing novel psychiatric drugs, including a lack of understanding of the brain and mechanisms for new drugs, relatively low government funding, and the risky nature of pharmaceutical investment within this therapeutic area. The report also describes regulatory and health system barriers to innovation.

Finally, the report presents a range of federal policy solutions that may help accelerate innovative drug discovery and development moving forward.

I. Background and Methods

Burden of Serious Mental Illness in the US

Serious mental illnesses are defined as mental, behavioral, or emotional disorders causing serious functional impairment that substantially limit one or more major life activities.[2] In 2020, approximately 6% of adults in the US (14.2 million people, or 1 in 20 adults) reported living with a serious mental illness.[1] The most common types of serious mental illness are schizophrenia (1% of adults), bipolar disorder (3%), and major depressive disorders (6%).[a 1, 3, 4] Individuals living with a serious mental illness have worse expected health, reduced education, and more limited career outcomes over the course of their life, combined with higher expected medical and societal costs.[11]

U.S. Adults with a SMI (2020)

14.2 MILLION

or **1 in 20**

Socioeconomic demographics

In 2020, young adults aged 18-25 had the highest prevalence of serious mental illness (9.7%) compared to adults of other ages (6.9% in ages 26-49, 3.4% in ages 50+). [1]

Approximately

5% of individuals living with **schizophrenia**,[52]

15% of those with recurrent **major depressive disorder**,[53]

and up to

20% of those living with **bipolar disorder**

will die by suicide.[54]

Bipolar disorder is equally prevalent across males and females,[37] schizophrenia is more prevalent in men,[38] and major depressive disorder (major depression) is more prevalent in women.[39] Mixed race adults have the highest prevalence of serious mental illness (9.9%), followed by American Indian/ Alaskan Native adults (6.6%), White (6.3%), Black (4.7%), Hispanic (4.5%), and Asian adults (2.0%).[b,1] The prevalence of serious mental illness is also increasing.[41] Among all adults, the prevalence increased from 3.7% in 2008 to 5.6% in 2020. Rate increases were highest for young adults ages 18-25 years, from 3.8% in 2008 to 9.7% in 2019.[1] In 2020, almost half (47%) of adults living with a

a These illnesses are not mutually exclusive

b These numbers reflect estimates of illness based on reported symptoms and severity in the National Survey on Drug Use and Health, although may underestimate prevalence since homeless populations not residing in shelters and institutionalized populations are excluded.

serious mental illness were not working, while the remaining worked full time (36%) or part time (17%).[1] In the same year, 22% of those living with serious mental illness had an income of less than 100% of the federal poverty level (FPL), while 25% and 53% had an incomes of 100-199%, and 200% or more of the FPL, respectively.[1] Adults living with mental illness in poverty face higher healthcare costs, decreased productivity, and poor general health, resulting in a greater socioeconomic burden.[42, 43]

Figure 1. Occupational Status for Those with a SMI, 2020

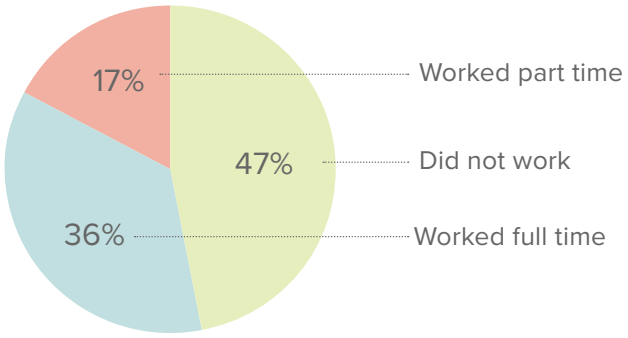
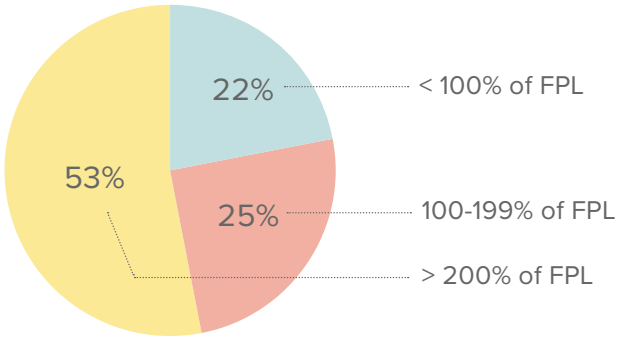


Figure 2. Income by % of Federal Poverty Level for Those with a SMI, 2020



In 2020, adults living with serious mental illness were most likely to be on private insurance (49%), Medicaid (25%), or another form of insurance (26%) including Medicare, Tricare, or Veterans Affairs health care.[c,1] Approximately 11% of individuals living with serious mental illness lacked any insurance.[1] Among adults living with serious mental illness enrolled in Medicare, 44% had dual eligibility for both Medicare and Medicaid in 2015.[44] Individuals over the age of 65 can qualify for both programs if they are low income. Those under age 65 can qualify for both programs if they are low income and have a qualifying disability that makes them eligible for Medicare (which can be demonstrated, for example, by having Social Security Disability benefits for 24 months).

The combination of disease and poverty makes the dual-eligible population one of the most vulnerable groups of individuals in the country. The Low-Income Subsidy program (funded through Medicare Part D) provides extra help for out of pocket prescription medication costs to those enrolled in Medicare with incomes below 150% of the FPL who also meet additional criteria. This program can be an important source of support for individuals living with serious mental illness. For example, it is estimated that more than 90% of individuals living with schizophrenia and 50% of those living with major depression who are enrolled in Medicare are eligible for the Low Income Subsidy program.[45, 46] Certain low-income individuals may also be eligible for Medicare Savings Programs that help with Medicare Part A (Hospital Insurance) and Part B (Medical Insurance) out of pocket payments.[47]

Health burden

The average life expectancy for individuals living with a serious mental illness is approximately 10 years less than those without a serious mental illness.[11]

This reduced life expectancy is due to increased mortality from both unnatural causes, including suicide and accidents, and natural causes.[48] Individuals living with serious mental illness have a range of physical and mental comorbidities that contribute to their poor health, decreased length and quality of life, and additional health care costs.

c Respondents could indicate multiple types of health insurance; thus, these response categories are not mutually exclusive.

For example, patients living with bipolar disorder or schizophrenia are four times more likely to suffer from chronic pain, and over 1.5 times more likely to suffer from hypertension or heart disease.[5] Patients living with a serious mental illness are also twice as likely to be diagnosed with diabetes.[6] In addition, one in four patients living with serious mental illness has a co-occurring substance use disorder.[7] As a result, total medical spending is approximately $100,000 higher for those with a serious mental illness over their lifetime, compared to those without.[11]

Living with a serious mental illness, particularly if untreated, is also a significant risk factor for suicide. The US has one of the highest suicide rates in the industrialized world at 13.9 suicides per 100,000 people in the general population, and this rate is even higher among those living with a serious mental illness.[8-10] Approximately 5% of individuals living with schizophrenia, [49] 15% of those with recurrent major depressive disorder, [50] and up to 20% of those living with bipolar disorder will die by suicide.[51]

As the coronavirus (COVID-19) pandemic has lingered in the US, its effects on the mental health crisis are becoming more evident. Twice as many individuals reported serious consideration of suicide in June, 2020 compared to 2018.[52] Adults reporting serious psychological distress increased four-fold between 2018 and 2020, and three-to-five times as many people reported symptoms of depression and anxiety in 2020 compared with 2018.[41, 53, 54] Not only has the prevalence of mental illness increased during the pandemic, but those with a history of mental illness have been shown to be at higher risk for severe illness from COVID-19.[55]

Economic burden

The annual per-person costs associated with serious mental illness is higher than other diseases like cancer and diabetes.[12] For example, the annual per-patient economic burden associated with schizophrenia, bipolar disorder and major depression has been estimated at $46,500, $21,000, and $14,000, respectively, including all direct and indirect costs of illness.

For those diagnosed with a serious mental illness by age 25, the associated lifetime costs can be as high as

$1.85 MILLION[11]

These estimates compare to an average annual per-patient economic burden of $3,200 for cancer and $12,000 for diabetes.[12]

The high economic burden of serious mental illness is driven in large part by high indirect costs. For bipolar disorder and schizophrenia, indirect costs are three and four times the direct costs of illness, respectively.[12] This phenomenon is reflective of the early age of onset and considerably high impact on productivity among individuals living with these conditions. Individuals living with a serious mental illness on average have lower educational attainment, and approximately half the lifetime earnings compared to individuals without serious mental illness.[11] The reduced ability to work also corresponds to an expected 500% increase in Social Security Disability Insurance (SSDI) payments and an 800% increase Supplemental Security Income (SSI) payments over the lifetime of those with serious mental illness, compared to those without.[11]

Societal consequences

Living with a serious mental illness is associated with increased risks of poverty, homelessness and interaction with the criminal justice system, with even higher risks among those living with co-occurring conditions such as substance use disorder.[13] These societal outcomes are due in part to the inadequate level of local health care and social services, and the likelihood that many people living with a serious mental illness have symptoms that go untreated.[13, 56] In 2020, the Department of Housing and Urban Development reported that approximately 20% of the 580,500 recorded homeless individuals in the US lived with a serious mental illness.[14] In addition, one study found that approximately one in four individuals diagnosed with bipolar disorder or schizophrenia were involved with the criminal justice system over a two-year period.[15] Rarely, however, are the interactions with the criminal justice system a direct result of an individual's mental health symptoms.[13, 57, 58] Instead, a person living with a serious mental illness may experience increased risk of interaction with law enforcement due to a lack of quality, accessible mental health care, poverty, a fragmented social safety net, and co-occurring substance use conditions.[13]

Living with a serious mental illness may also impact relationships, as many individuals depend heavily on help from informal caregivers, typically family and friends, due to the debilitating nature of their illness.[16]

Over eight million Americans are unpaid informal caregivers to someone living with a mental illness.[16]

Caring for and caring about an individual living with a serious mental illness can decrease an individual's quality of life and productivity, and can increase financial strain.[16, 59] Informal caregivers often provide support by arranging or providing transportation, helping with shopping, housework, meals, and finances, and arranging health care services for their loved one living with a serious mental illness (e.g., making appointments).[16] Informal caregivers of individuals living with a serious mental illness provide, on average, 32 hours of care each week.[16] Time devoted to care for a loved one has a substantial impact on overall costs related to serious mental illness. In 2020 in the US, informal caregiver costs for schizophrenia alone were estimated to total $83.7 billion in unpaid caregiving and $20.8 billion in additional costs, including personal health care costs.[3] Balancing between caregiving and work can be difficult for many caregivers, with half of caregivers reporting that they arrived to work late, left work early, or took time off in the past year in order to provide care for a loved one living with a serious mental illness. As a result of their responsibilities, informal caregivers are more likely than non-caregivers to be unemployed or work fewer hours.[17]

Caregivers of individuals living with mental health conditions report elevated levels of emotional stress (53%) and physical strain (25%).

These rates are higher than caregivers of individuals who are not living with a mental health condition.[16]

Methods

To develop this report, we conducted a literature review to identify articles documenting barriers and policy options that were associated with pharmaceutical innovation. We queried PubMed, EMBASE, PsycInfo and PAIS Index for published and unpublished articles. We used combinations of the following terms to generate a search: health services needs and demands, pharmaceutical

research, incentive, healthcare policy, and pharmaceutical innovation. We reviewed all articles post-year 2000 for relevance, and we compiled key articles to inform the report. Using the OpenGrey and The Grey Literature Report databases, we also conducted a grey literature search with similar search terms.

In order to best assess current field perspectives on pharmaceutical innovation in serious mental illnesses, we also conducted 18 stakeholder interviews using a semi-structured interview guide via video conference. Interviews we conducted between June and July of 2021, and each interview took between 30-60 minutes. Stakeholders were recruited through convenience sampling. We contacted individuals from organizations that we identified as having an established interest in health services research, serious mental illness, and/or pharmaceutical innovation. These stakeholders included representatives from advocacy and government organizations, as well as health services and health policy researchers, physicians, attorneys, and government organizations. Stakeholders were not compensated for their participation.

II. Unmet Need in Serious Mental Illness

While beneficial treatments exist for schizophrenia, major depression, and bipolar disorder, it is often a challenge for patients to find an effective and tolerable treatment regimen to manage their specific condition, in part due to the underlying heterogeneity and complex biology underpinning mental health conditions.[18-20] Medications commonly cause unwanted side effects, which are associated with patient non-adherence.[21] Not all patients will achieve an adequate response to treatment, and many continue to live with symptoms of their disorder, resulting in continued functional impairment.[22, 23] In addition, patients who are prescribed certain treatments, such as antipsychotics, may develop associated conditions as a result. Such conditions include metabolic disorders and drug-induced movement disorders that can further add to the burden of illness and necessitate additional treatment. Accordingly, there remains a strong and urgent need for new therapies to treat these conditions.

Schizophrenia

Individuals living with schizophrenia can suffer from a combination of positive, negative, and cognitive symptoms. Positive symptoms can include hallucinations, delusions, or disordered thinking. Negative symptoms can include reduced motivation, diminished pleasure and emotion, and reduced speaking. Individuals with cognitive symptoms typically have trouble processing information or focusing.

Schizophrenia requires lifelong treatment, including medication. Antipsychotic medications are typically used as first-line treatment for patients. Treatment for schizophrenia is based on individual symptoms which vary among patients, and it is often challenging to find the optimal medication or combination of medications for any given patient.[61]

On average, there is a nine-year gap between when patients experience their first episode of schizophrenia and when they initiate treatment.[60]

Once treatment is initiated, 60% of individuals experience a reduction in their delusions, hallucinations, and cognitive deficits associated with schizophrenia.[62] However, the majority of patients continue to experience residual symptoms of the disease, including negative symptoms and cognitive impairment, which do not respond well to currently available antipsychotic treatments.[63-66]

Further, medications prescribed for schizophrenia may cause side effects, such as weight gain, sedation, cardiovascular risks, and changes in mood, that can lead to intolerability and reduce adherence.[67] Due in part to these side effects and potential lack of comprehensive symptom control, non-adherence rates for patients living with schizophrenia can range between 27% and 69%.[68] The impact of non-adherence in those living with schizophrenia can be substantial—non-adherence is linked to increased rates of relapse with critical consequences, including increased risk of suicide and hospital re-admission.[69, 70]

Prolonged use of antipsychotics, which occurs most commonly in schizophrenia but can also be part of a treatment regimen for major depression and bipolar disorder, may lead to the development of drug-induced movement disorders, including tardive dyskinesia, a disorder characterized by uncontrollable, abnormal, and repetitive movements of the face, torso, and/or other body parts. The symptoms of tardive dyskinesia may be persistent and potentially disabling, adding to the disease burden among patients living with serious mental

illness.[71] In addition, recent studies have linked the treatment of schizophrenia with anticholinergic drugs to a reduction in cognitive function.[72] Despite the risks associated with antipsychotics, however, there is international consensus that the benefits of these medications for patients living with schizophrenia outweigh the potential side effects.[73] However, 40% of individuals living with schizophrenia are untreated in any given year.[24]

Bipolar disorder

Bipolar disorder is a lifelong illness in which individuals experience unusual shifts in mood, energy and activity level, and ability to think clearly. There are three types of bipolar disorder, which differ based on the duration and intensity of these symptoms.[74]

From the time of symptom presentation, the average time until patients receive a diagnosis of bipolar disorder is nearly six and a half years.[75]

Once diagnosed, finding appropriate treatment can be challenging. Medications currently prescribed to manage bipolar disorder can include mood stabilizers, antipsychotics, antidepressants, and/or anti-anxiety drugs.[76] Each treatment regimen is based on individual symptoms, which can vary greatly among patients, and it often takes trial and error to find the right medication or combination of medications. For those able to find and adhere to an effective regimen, there is still risk of relapse into mania or depression. In a large pragmatic trial that treated bipolar patients according to current treatment guidelines, over half of participants (58%) achieved recovery using one or more medication regimens. However, over the following two years, approximately half of these patients subsequently experienced a recurrence of their symptoms.[77]

Medications prescribed to treat bipolar disorder are associated with side effects, such as weight gain, sedation, dry mouth, increased glucose and lipid levels, vision changes, dizziness, drug-induced movement disorders, and more.[78] As with other serious mental illnesses, non-adherence is common due to medication side effects, as well as the complexity of medication regimens, comorbid conditions, substance use, and lack of patient education.[79] Within a period of 10 days, 34% of patients living with bipolar disorder reported missing at least one dose of their medication, 20% missed at least one entire day of medication, and 2.5% missed all doses for 10 days.[80] Over half (51%) of those living with bipolar disorder are untreated in any given year.[26]

Major depressive disorder

Those living with major depression have persistent feelings of sadness and loss of interest, and often also have severe problems with sleep, eating, concentration, and feelings of worthlessness.[81] Over two-thirds of individuals living with major depression have severe impairment that limits life activities.[82] These include activities of daily living, sustaining relationships, and work capacity and productivity.[83]

The impact of major depression in terms of functional status and overall wellbeing has been shown to be equal or greater of that of other severe chronic conditions like diabetes and congestive heart failure.[84]

The duration of illness can vary from one episode of major depression lasting several months, to a lifetime of recurrent episodes.

Major depression is typically treated with

psychotherapy, medications, or both. Antidepressants are the first-line medication for those living with major depression. However, less than 30% of individuals living with major depression reach remission during their first trial of an antidepressant.[20] Clinicians may choose adjunctive treatment, including antipsychotics, when patients do not respond sufficiently to treatment with antidepressants.[85] Major depression's heterogeneity in symptoms and disease presentation highlight the inability for a "one-size-fits-all" approach to treatment. [20] In a large pragmatic clinical trial of patients living with major depression treated according to guidelines, 67% achieved remission after trying one or more medications.[86] However, relapse rates are common among patients who achieve remission, and can range between 40-70% based on the treatment regimen of the patient.[23]

Non-adherence is associated with an increased risk of relapse, recurrence, emergency department visits, and hospitalizations.[87] Studies have shown that almost 70% of patients are non-adherent with their antidepressants, including those that miss doses and those that discontinue their medication prematurely.[88] Reasons for non-adherence vary, and include patient, clinician, and health system-related factors. Some patients are non-adherent to antidepressants due to side effects of the medications, which may include weight gain, sexual dysfunction, drowsiness, low blood pressure, and gastrointestinal toxicity.[89] For persons prescribed long-term antipsychotics to manage major depression, other side effects can include drug-induced movement disorders.[90] In any given year, approximately 35% of adults living with major depression are untreated for major depression.[25]

III. Brief History of Biopharmaceutical Innovation within Serious Mental Illness

Despite high unmet need, the development of novel pharmaceuticals in serious mental illness has lagged behind advancements in other disease areas over the last 30 years. Most new medications that have entered the market have largely benefitted patients through increased tolerability, or alternative routes of administration (e.g., injection instead of pill), compared to earlier generation treatments.[91] While these advancements have provided incremental benefit to certain patients, new treatments that are effective in treating symptoms and improving the wellbeing of patients living with serious mental illness are urgently needed.

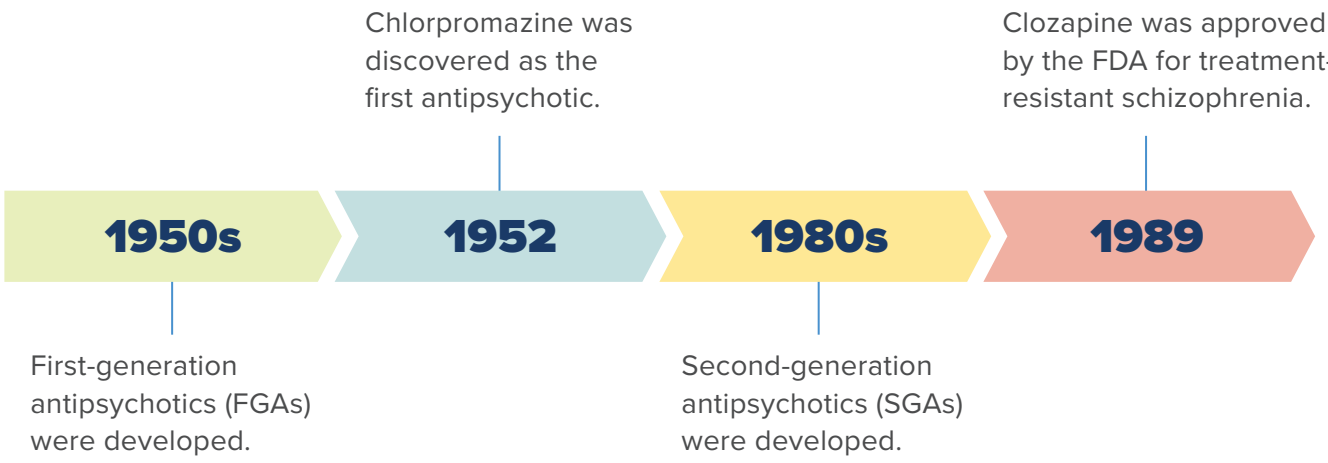
Schizophrenia

The first antipsychotic, chlorpromazine, was discovered in 1952 following its use for pre-operative anesthesia, and is still used occasionally in practice today.[27] Chlorpromazine and therapies that followed are considered first-generation antipsychotics (FGAs), also known as neuroleptics. These FGAs consist of both low- and high-potency therapies with varying side effects. Low-potency FGAs (chlorpromazine and thioridazine) are associated with a wide array of side effects including sedation, blurred vision and urinary retention, but have lower risk of drug-induced movement disorders, like tremors, impaired speech, tardive dyskinesia, and other involuntary movements.[92] High-potency FGAs (fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, and tifluoperazine) are associated with lower levels of sedation, weight gain, and anticholinergic activity, but carry a higher risk of drug-induced involuntary movement disorders.

Second-generation antipsychotics (SGAs), also known as atypical antipsychotics (aripiprazole, clozapine, risperidone, olanzapine, quetiapine, risperidone, sertindole, ziprasidone, and zotepine), followed in the 1980s. Clozapine was approved by the US Food and Drug Administration (FDA) in 1989 for treatment-resistant schizophrenia (TRS), and remains the most effective treatment for TRS today.[93, 94] Four SGAs are more effective than FGAs in positive and negative symptom control (amisulpride, clozapine, olanzapine, and risperidone), and the remaining are equally effective.[95]

Each SGA has a varying side effect profile, and often the appropriate treatment is chosen based

Figure 3. Key advancements in biopharmaceutical innovation for schizophrenia



on tolerability. Side effects may include weight gain, hypotension, sedation, cardiac effects, sexual dysfunction, tardive dyskinesia, and seizures.[96] SGAs generally have a lower, though non-insignificant, risk of drug-induced movement disorders, such as tardive dyskinesia, compared to FGAs.[96, 97]

Some of the above-referenced FGA and SGA therapies have recently become available as long-acting injectable antipsychotics, given as intramuscular or subcutaneous injection.[98] These injections are given every few weeks, and may be the preferred option for individuals with low adherence rates.[99]

Bipolar disorder

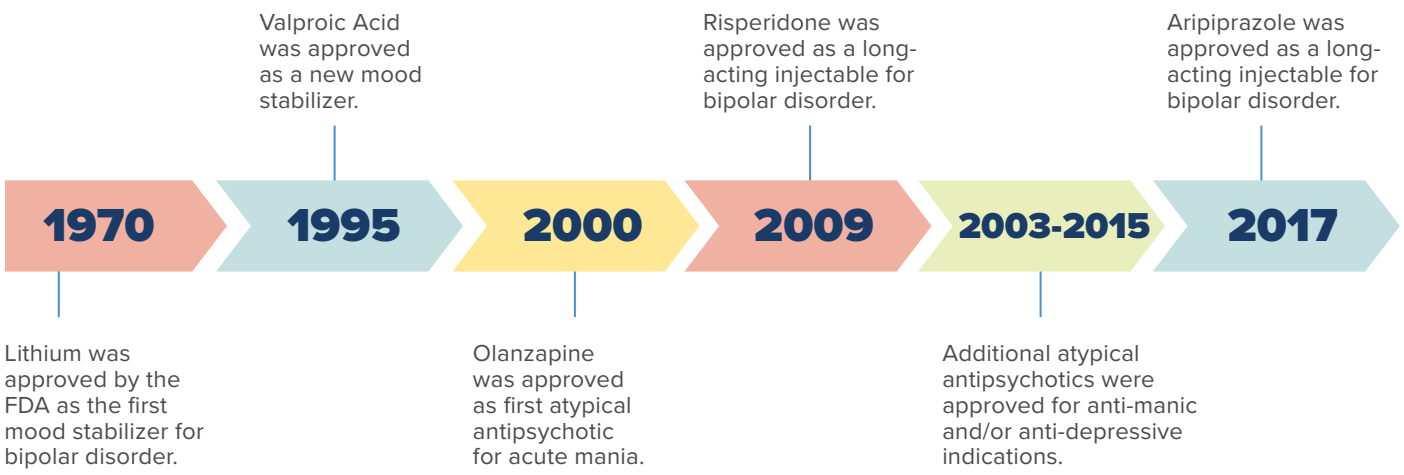
Individuals living with bipolar disorder were often treated with barbiturates until the approval of lithium in the early 1970s. Lithium was the first mood stabilizer approved by the FDA and was the only effective treatment available until the mid-1990s when valproic acid, an anticonvulsant agent, was approved.[100] Carbamazepine and lamotrigine, both antiepileptic drugs, were later approved for their mood-stabilizing effects.

Olanzapine was the first atypical antipsychotic drug approved for treating acute mania in bipolar, in 2000. Additional atypical antipsychotics (i.e., risperidone, quetiapine, ziprasidone, aripiprazole, asenapine, cariprazine, lurasidone, and onlanzapine-fluoxetine) were later approved between 2003-2015 for anti-manic and/or anti-depressive indications in bipolar disorder.[101] Risperidone and aripiprazole became available as long-acting injectables for bipolar disorder in 2009 (initial approval 2003) and 2017 (initial approval 2013), respectively.[100] Over the past 20 years, the use of mood stabilizers in bipolar disorder has decreased, while the use of antidepressant and atypical antipsychotic treatment has increased.[102] Because of the complex nature of bipolar disorder, treatment regimens must be tailored to each individual's unique symptoms, and different regimens exist for manic episodes, depressive episodes, and maintenance therapies.[100]

Major depressive disorder

Many classes of antidepressants are available for the treatment of major depressive disorder, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants that don't fit into other categories.[103] MAOIs were the first antidepressants developed; they were originally developed to treat tuberculosis until it was discovered that side effects from these inhibitors improved symptoms often associated with major depression, such as improved mood and increased appetite.[104] MAOIs were officially explored

Figure 4. Key advancements in biopharmaceutical innovation for bipolar disorder



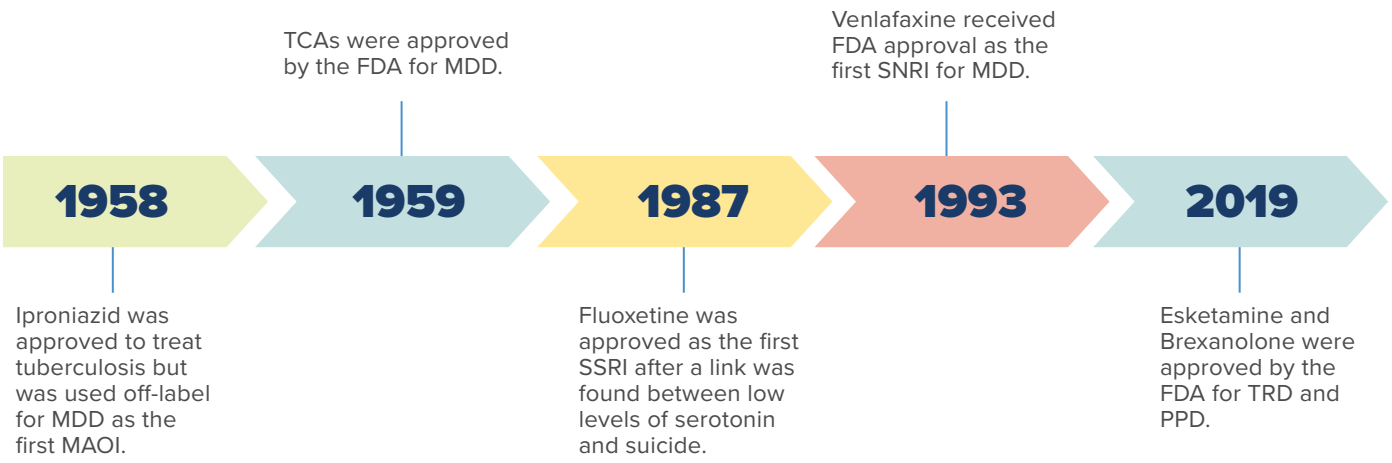
as a means to treat major depression in the late 1950s, although their use today is limited by safety concerns, including hypertensive crises when taken with certain foods and medications.[104] In 1959, the FDA approved TCAs to treat major depression.[104] TCAs work by inhibiting norepinephrine and serotonin reuptake, which leads to an increased concentration of these neurotransmitters in the synaptic cleft.[104]

In the mid-1970s, research began to emerge on the antidepressant effects of SSRIs, after a link was found between low levels of serotonin and suicide. The FDA approved fluoxetine in 1987 as the first SSRI. Venlafaxine later received FDA approval in 1993 as the first SNRI designed to treat major depression. While SSRIs block serotonin reuptake, SNRIs stop the reuptake of both serotonin and norepinephrine transporters. SNRIs may show some improvement in treating major depression when compared to SSRIs, but this improvement is minor.[104]

Two recent drug approvals have offered hope to individuals living with major depression. In 2019, esketamine was approved by the FDA for treatment-resistant depression and brexanolone was approved for post-partum depression.[105, 106] Esketamine, the first therapy with a new mechanism of action indicated for the treatment of major depression in nearly 30 years, was derived from extensive research on the anti-depressant effects of the existing anesthetic ketamine.[107] Truly novel therapy, the approved ketamine derivative is a nasal spray administered to patients living with treatment-resistant depression in a certified office or clinic setting, and is given in conjunction with an oral antidepressant.[108] Esketamine has been shown to decrease the risk of relapse by 51% among patients who achieve stable remission (symptom-free state) and 70% among patients who achieve stable response (improvement following treatment).[109] Although the research into the drug's mechanism of action is evolving, it is thought to target N-methyl-D-aspartate (NMDA) receptors and alter the function of interneurons in the brain.[110] There is ongoing research exploring other ketamine derivatives and similar brain pathways.[111, 112]

Brexanolone is a similarly revolutionary product and the first FDA-approved treatment specifically for post-partum depression (PPD). Prior to its approval, many of the standard therapies for major depression were also used for PPD.[113] Brexanolone was developed based on the hypothesis that allopregnanolone, a metabolite of progesterone that decreases sharply after childbirth, may play a part in the pathway to PPD.[114] Brexanolone is an aqueous formulation of allopregnanolone that is administered by IV infusion and has been shown to significantly reduce depression scores compared to placebo at 60 hours post-treatment.[115] Similar to esketamine, its discovery and approval was an important step forward in developing novel therapies for serious mental illness.

Figure 5. Key advancements in biopharmaceutical innovation for major depressive disorder



IV. Barriers to Innovation in Mental Health

A number of barriers have contributed to the slow progress in researching and developing new drugs for serious mental illness. We will focus on: scientific and research barriers, regulatory barriers, and health system barriers. There are large societal benefits to treating serious mental illness, but researchers have been hindered in their development efforts by gaps in their understanding of the biology of the brain. This has slowed progress in identifying new mechanisms of action and psychiatric drug targets. As a result, clinical trials carry a higher than average risk of failure, and market protections are not sufficient to incentivize much of industry to invest in the therapeutic area. In addition, health system barriers, such as lower net revenue for the large segment of the serious mental illness population with Medicaid insurance, may further discourage investment.

Scientific Barriers

Major scientific contributors to the lack of progress in developing drugs for serious mental illness include: (1) limited knowledge of disease mechanisms and promising drug targets, (2) lack of biomarkers that could serve as objective measures of serious mental illness, both for diagnosis and evaluating treatment response, and (3) lack of adequate animal models to inform molecular target selection and validation and testing of treatment efficacy.[27]

The complexity of studying the brain and its basic mechanics is a fundamental challenge to identifying molecular targets that could advance drug development for serious mental illness. The field of basic neuroscience has made strides in identifying neurotransmitters and their receptors, understanding the molecular machinery of cells in the central nervous system, the circuitry of these cells, how they develop, and their role in behavior, and the mechanisms by which cells maintain a functional state.[116] Despite this progress, there is limited understanding of these processes in serious mental illness, which impedes the identification of new drug targets. In fact, molecular targets for the drug classes most commonly used to treat serious mental illness today are the same as their 1950s predecessors.[27] Therapies targeting the central nervous system must also must cross the blood-brain barrier, which presents yet another challenge for drug development.[117]

The limited knowledge of neurochemical pathways in serious mental illness, along with the wide range of symptoms within these conditions has also made it difficult to identify biomarkers that can aid in diagnosis and treatment.[118] A biomarker is a defined characteristic that can be measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention (as compared to clinical outcome assessments, which measure how a person feels, functions, or survives).[119] Examples of biomarkers include laboratory test results and heart rate and blood pressure readings. Recently, genetic and genomic biomarkers are being explored in support of precision medicine. While researchers have identified potential biomarkers for use in serious mental illness, there are currently no biomarkers that are used in clinical practice, and thus no way to "objectively" diagnose individuals or assess the efficacy of treatments.[118] The lack of biomarkers in mental health research has made proof-of-concept and larger trials more difficult to conduct. Diagnoses and the efficacy of therapies are still measured clinically with validated, but often "subjective," clinical outcome measures like tests of motivation, attitude, and cognition, in which assessment methods and results may vary between clinicians.[120] The reliance on these imprecise scales for diagnosis and measures of efficacy is known to contribute to the costly failures within clinical trials

for serious mental illness. [27]

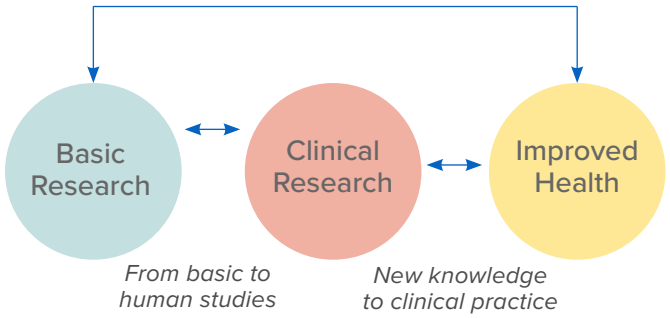
Unlike other organs, the human brain is difficult to examine directly. Animal models are thus critical for target validation when testing new therapies, but development of such models for testing neuropsychiatric drugs is extremely complex. There is little similarity between animal models and humans in terms of molecular pathways, cells, and circuits in the brain.[27, 29, 121, 122] In addition, treatments are evaluated in animals based on behavioral endpoints, due to the previously discussed lack of biomarkers for mental health conditions. While these behaviors in healthy animals or disease models may mimic certain symptoms of psychiatric disorders, the underlying mechanisms remain unknown. As a result, treatments that demonstrate efficacy based on these behavioral endpoints in animals often lack corresponding efficacy in humans, leading to repeated failures in human clinical trials.[27] Innovation in this area would benefit greatly from improved animal models, but so far developing useful models has proven to be a major challenge.

Research Barriers

Therapeutic advances require investment and collaboration from a multitude of public and private actors throughout the spectrum of drug discovery and development. Medical innovation starts with basic science research, progresses through clinical trial research, and continues throughout the lifecycle of a marketed product, with post-market studies and pharmacovigilance activities. The federal government funds most basic science research through intramural research at government agencies (e.g., the National Institute of Health (NIH)) and funds extramural research at research institutions, such as universities and medical centers. This research largely focuses on expanding the foundational knowledge of how diseases develop and are transmitted, including the preclinical studies that can improve our understanding of the biochemical mechanisms underlying brain functions.

Biopharmaceutical companies initiate and fund the majority of clinical research in the US.[28] Clinical research translates findings from basic science research into new drug candidates that are tested on human volunteers to assess safety and efficacy. Data from clinical research can eventually be used to support marketing approval by the FDA. Drug development, however, is not a linear process. While basic science promotes innovation in clinical research by identifying fundamental elements for scientific understanding, clinical research also informs basic science research when the knowledge gained in a clinical trial further guides research into the fundamental biology of the disease.

Figure 6. Interdependency of basic and clinical research [d,e]



d SSANKELLA. Bench to bedside: A journey of basic science to clinical research. 2017 [cited 2021 December, 21]; Available from: https://speacatutsw.wordpress.com/2017/03/13/bench-to-bedside-a-journey-of-basic-science-to-clinical-research/.
e Zerhouni, E.A., Translational research: moving discovery to practice. Clinical Pharmacology and Therapeutics, 2007. 81(1): p. 126-128.

Government-funded research

To facilitate drug development for serious mental illness, there is a crucial need for the federal government to do more to support research through the NIH. Most of the NIH research on serious mental illness is funded through the National Institutes of Mental Health (NIMH). [123] Between 2016 and 2021 there was an increase in funding to the NIMH, with additional funding allocated to support research on

serious mental illness.[124] In 2021 an estimated $540 million dollars was spent at the NIH to fund research for serious mental illness, or $42 for each individual living with serious mental illness in the US.[124]

Compared to other disease areas, NIH funding for research in serious mental illness is disproportionately low, especially considering the prevalence and significant burden of illness. For example, sexually transmitted diseases (excluding HIV) received a greater amount of NIH funding in 2021 when compared to schizophrenia, ($404 versus $266 million, respectively), despite schizophrenia having a significantly higher disease burden in the US. Dental/oral disease and tuberculosis also received a greater amount of NIH funding in 2021 ($638 and $493 million, respectively), despite schizophrenia having a higher burden of disease.[12, 124, 125]

Between 2015 and 2020

239 clinical trials for new medications for SMI

vs.

5,264 clinical trials for new medications for CANCER

In addition, the NIMH has been criticized for spending a large majority of its funding on basic research with little funding for clinical research.[126] Because no other government-funded institution except for the US Department of Veterans Affairs is engaged in clinical mental health research, including research on non-pharmaceutical treatments, there is an even greater need for the NIMH to have a larger role in funding clinical research.[126] Referring to this historical allocation of resources toward basic research, a long-serving former director of the NIMH acknowledged in 2017 that while the NIMH focused on the neuroscience and genetics of mental health disorders under his leadership, not enough was done to help the people currently living with mental illness, stating "I don't think we moved the needle in reducing suicide, reducing hospitalizations, improving recovery for the tens of millions of people who have mental illness."[126] Clinical research funded by the NIMH is mainly focused on evaluating interventions that may not attract the interest of pharmaceutical industry funding. These include behavioral interventions, such as interventions to improve patient adherence to medication, patient engagement with their care providers, and non-pharmaceutical treatments like psychotherapy. The federal government has also been the largest funder of trials comparing behavioral interventions to pharmaceuticals, or other interventions like transcranial magnetic stimulation.[127] These studies are important to identify a full range of options that may benefit patients. The knowledge gained in these studies can also inform industry research and development, as more knowledge is acquired about the real-world effectiveness of pharmaceutical interventions.

Industry funded research and development

While the societal benefits of new and effective therapies for serious mental illnesses are extensive, clinical research in this space has lagged compared to other disease areas, largely due to the limited knowledge available on brain mechanisms and targets. As a result of these substantial knowledge gaps, clinical trials in serious mental illness take longer and are less successful than in other disease areas.

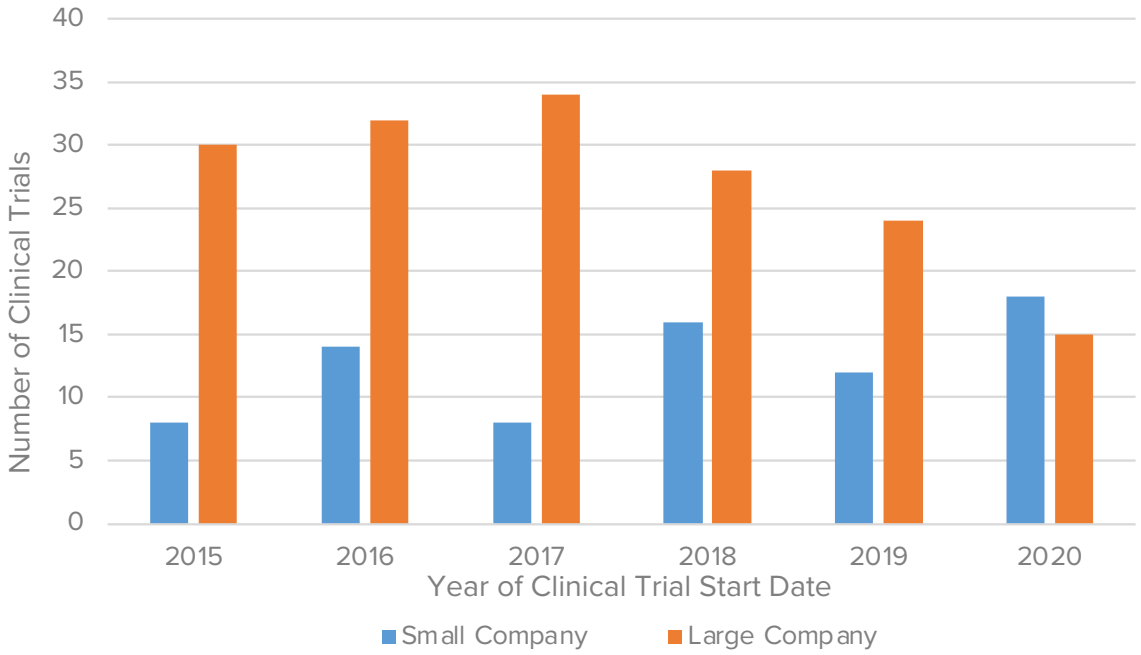
On average, it is estimated to cost between $1 and $2+ billion USD to bring a new drug to market, including pre-clinical and clinical research, and FDA review.[128] This includes capital costs, and expenditures on drugs that fail to reach the market.[128] However, these estimates vary by clinical area. Clinical development timelines for drugs used to treat severe mental illness are some of the longest. For example, anticonvulsants, often used to treat bipolar disorder, have an average clinical research period of 8.1 years, antidepressants average 8.5 years, and antipsychotics 8.6 years.[129]

This compares to an average clinical development time of 6.5 years for drugs across all chronic illnesses, and shorter times for acute illnesses.[129] In addition, clinical trial success rates are low: only 6.2% of drugs for the central nervous system (CNS) that enter into clinical trials, including drugs for serious mental illness, achieve market approval.[130] This compares to 13.3% for non-CNS drugs. [130] In addition, the FDA approval process is 38% longer for CNS versus non-CNS drugs.[131] Extended research times and low success rates result in increased costs. When CNS drugs fail, they tend to do so in late-stage trials and after significant financial investment. This often results in a financial risk that pharmaceutical companies are unwilling or unable to take.[132]

As a result of these barriers, as well as others not included in this report, over time many large pharmaceutical companies have shifted investment away from serious mental illness,[29] in favor of other therapeutic areas where well-defined disease biology, biomarkers, and drug targets make research and development more attractive. Research programs in mental illness among large-market cap pharmaceutical companies fell by as much as 70% from 2006-2016, with many pharmaceutical companies deciding to focus in other disease areas.[133] In cancer, for instance, it is estimated that in 2014, for each $1,000 in disease burden cost, industry spent $75.50 on pharmaceutical development. In mental illness, it was much lower. Schizophrenia had an industry investment of $3.10 per $1,000 in disease burden cost, major depressive disorder was at $1.80, and bipolar disorder was at $0.40.[12]

In the absence of sustained investment from large pharmaceutical companies, many smaller biotechnology and pharmaceutical firms have entered this market space. Between 2015 and 2020, 239 clinical trials at any phase were conducted by the pharmaceutical industry, including both large and small firms.[30,f] Over this time,

Figure 7. Sponsorship of Clinical Trials for Serious Mental Illness by Company Size, 2015-2020



Note: Company size was considered "Small" if employee number was ≤ 500[g]

f This compares to 5,264 cancer trials that were funded during this time frame.

g The federal government generally defines a small business as one with fewer than 500 employees [134]. U.S. Small Business Administration. Federal Contracting: Basic Requirements. Accessed January 4, 2022. https://www.sba.gov/federal-contracting/contracting-guide/basic-requirements

smaller biotech and pharmaceutical companies have steadily increased their sponsorship of clinical trials for serious mental illness, while larger pharmaceutical sponsorship declined (Figure 7[30]). Smaller firms often obtain funding from venture capitalists and other life science investors, including larger pharmaceutical companies, and are more suited to make riskier investments, and more quickly abandon failing projects.

When preclinical and early clinical studies in smaller firms succeed or show promise, larger pharmaceutical companies may look to acquire these firms through mergers and acquisitions, or develop product licensing agreements. This interdependence between larger and smaller companies is key to innovation in mental health, and in 2018 CNS drugs were one of the most researched products among smaller pharmaceutical companies, lagging only behind oncology.[135] However, it is yet to be seen whether the growing investment in mental health among smaller companies can fully compensate for the exit of larger firms.

Clinical trial recruitment and retention

Serious mental illness is a particularly difficult area to conduct clinical research in, especially with regard to recruitment and retention in trials, creating another barrier to innovation.[136] During disease onset and early in diagnosis, individuals may have difficulty accepting their diagnosis and initiating treatment, and be less willing to seek participation in clinical trials.[137] Enrolling in a clinical trial also requires additional clinic visits that can significantly impact a work or academic schedule, and has been shown to be a significant barrier to research participation. Even for participants enrolled in trials, retention is a challenge. Over the course of a study, participation often declines due to lack of response to a therapy, side effects, or the extensive appointment schedule.[138, 139] This is particularly challenging in a population where many individuals have significant functional or cognitive impairments that may limit their ability to get to and from appointments, navigate a complicated health care system, and/or actively and reliably participate in clinical research.[140]

Regulatory Barriers

Patent and exclusivity protections

The US incentivizes pharmaceutical investment with periods of market protection, to cover the costs of research and development and provide a return on investment. The US government awards medical product developers protection against competition through two primary mechanisms: (1) a period of patent protection, and (2) market exclusivity following regulatory approval.

The US patent system protects the intellectual property associated with a new drug. A drug developer typically seeks a pharmaceutical patent during research and development. This protects drug developers from competitors who may wish to market the newly discovered entity. The typical patent award is 20 years, starting from the time the patent application was filed. This means that after a drug enters the market many years later, the remaining patent protection is often less than 20 years. In order to compensate for the time spent in clinical trials, the Hatch-Waxman Act was passed into law in 1984 and allows pharmaceutical manufacturers to petition for extension of the patent term by one-half of the time from clinical trial initiation to filing with the FDA, plus FDA review time, capped at five years.[141]

The fixed patent cap at 20 years, plus the fixed maximum patent life restoration of five years afforded through Hatch-Waxman, could discourage the development of drugs that require longer than average pre-clinical and clinical research.[35] This creates a paradox in drug innovation in that pharmaceutical research and development is incentivized with a post-market exclusivity reward, but the longer the research takes, the lower the reward post-market.[129] The one-size-fits-all reward across innovations, with a few exceptions, will naturally over-reward some therapies and under-reward others, including drugs for serious mental

illness.[129, 142]

Pharmaceutical products are also protected by periods of market exclusivity following FDA approval. Prior to the enactment of the Hatch-Waxman Act in 1984, the US patent system was the only protector of market exclusivity. With this Act, in addition to modifications to the patent life extensions detailed above, a new exclusivity was established to incentivize drug innovation. Specifically, the Hatch-Waxman Act created a five-year period of market exclusivity following FDA approval of a new drug that qualifies as a new chemical entity. During this time, the FDA cannot approve a generic version of that drug, even if the patent term has expired.

Since the enactment of Hatch-Waxman, additional, targeted regulatory exclusivity periods have been implemented to incentivize the production of drugs in certain clinical areas with significant unmet need that would otherwise be overlooked. This includes drugs indicated for rare diseases (known as orphan drugs), antibiotics, and pediatric indications. At the present time, however, no exclusivities exist for psychiatric or other CNS drugs that face long development times and could benefit from lengthened exclusivity periods.

Accelerated approval

In 1992, the FDA initiated the Accelerated Approval program to speed access to drugs with significant unmet need. This allows drugs that are developed for serious conditions without effective therapies to be approved based on a surrogate endpoint, --for example a biomarker of disease, --instead of changes in clinical outcomes. Examples of surrogate endpoints include changes in blood glucose levels as a marker for changes in diabetes, or changes in viral load as a surrogate for the progression of HIV/AIDS. In 2012, Congress passed the FDA Safety and Innovation Act that expanded accelerated approval to apply to drugs that improve an intermediate clinical endpoint. An example of an intermediate clinical endpoint includes blood pressure as a predictor of stroke and myocardial infarction.

For surrogate or intermediate endpoints to be considered eligible for accelerated approval, there must be evidence that changes in the endpoint will predict changes in long-term outcomes. Companies that have a drug indication approved through accelerated approval are required to conduct confirmatory studies that demonstrate changes in the long-term clinical endpoint.

Accelerated approval has served as an important means for many patients with high unmet need to access treatment earlier than would be possible with the traditional approval process.

Accelerated approval cannot be used for therapeutic areas that do not have established surrogate or intermediate endpoints, including serious mental illness.

As a result, accelerated approval has not had an impact on expediting access to new drugs for these conditions.

Health System Factors

Pharmaceutical company investment in new drug candidates is driven in large part by the expected return on their investment.[31-33] The return on investment is the lifetime global revenue earned from a drug, minus the company's overall cost to develop, market, and monitor the drug once on market. Expected revenue is determined by the expected volume of sales over time, as well as the net amount that a pharmaceutical company is reimbursed for these sales.

As discussed earlier, developing a drug for serious mental illness comes with higher costs and risks compared to drugs in other therapeutic areas. In addition, there are aspects of the current health care system that may limit revenue generated from mental health drugs. These include the relatively

low proportion of patients living with serious mental illness who obtain treatment compared to other disease areas, and the relatively high proportion of treated patients who are insured through Medicaid, which pays lower than average prices for pharmaceuticals. High expected costs and the potential for low expected revenues may discourage companies to invest in serious mental illness.

Health system barriers to seeking and receiving treatment

The relatively high proportion of individuals living with serious mental illness that are not on treatment limits the potential market for new drugs. Forty percent of patients living with schizophrenia, 50% of patients living with bipolar disorder, and 35% of patients living with major depression are not on treatment.[24-26] Stigma plays a significant role in the limited number of individuals living with serious mental illness who seek treatment, as many worry about public opinion and discrimination. The limited supply of mental health clinicians also restricts the number of patients who can seek specialized care for their illness. Ninety-six percent of counties in the US have reported an unmet need for prescribers in psychiatry.[143] This includes providers in private practice, along with those in federally qualified health centers, rural health centers, and community mental health clinics, all of which provide important services to low-income individuals living with serious mental illness. Exacerbating this unmet need is the high average-age of psychiatrists, with 55% of psychiatrists aged 55 or older and expected to retire within 10 years, compared to 38% in other disciplines.[143] Without sufficient specialists available to diagnose and provide treatment to those living with serious mental illness, patients have limited access to novel treatments.

Reimbursement challenges

Many more individuals living with serious mental illness are covered by Medicaid (25%) or are uninsured (11%) compared to the US average. [1] State Medicaid programs are required to cover nearly all FDA-approved drugs; in exchange, manufacturers must enter into a statutorily-defined rebate agreement that guarantee the Medicaid program pays a price at least as low as the "best price" provided to other health care payers.[h] As a result, net revenue from drugs reimbursed under Medicaid is generally lower than drugs reimbursed under most other private and public insurers. In 2017, for example, the average net price for top selling drugs in Medicaid was 65% lower than the average net price in Medicare.[34] The relatively large number of patients living with serious mental illness on Medicaid thus potentially limits the revenue companies may expect for new drugs, and may be a disincentive to investment in this space.

h This policy states that for brand name drugs the manufacturer must provide the Medicaid program with a rebate equal to 23.1% of the Average Manufacturer Price (AMP) or the difference between AMP and "best price," whichever is greater. Best price is defined as the lowest available price to any purchaser – including wholesalers, retailers, providers, but excluding certain government programs, including Part D plans and the health program for veterans. AMP is defined as the average price paid to drug manufacturers by wholesalers and retail pharmacies. For generic drugs, the rebate amount is 13% of AMP, and there is no best price provision.

V. Policy Solutions

In this section we will outline proposed policy solutions that may help to overcome the scientific, research, regulatory, and health system barriers outlined above, to help drive innovation in serious mental illness.

Policy Solutions to Target Scientific and Research Barriers

NIMH research funding

As discussed in Section IV, NIH funding allocated towards serious mental illness is disproportionately low considering the significant unmet medical need and tremendous burden that serious mental illness places on patients, caregivers, and society.

The level of NIH funding devoted to researching serious mental illness should be increased so that it is proportionate to the burden of these illnesses.

In addition, additional funding that is allocated to the NIMH over the coming years should be used to increase the level of clinical research conducted at the institute, which has declined in the last decade. The need for more effective treatments in serious mental illness exists among patients right now, and while the current focus of the NIMH on basic science is important for long-term progress, clinical research is also necessary to help patients.

Additional NIMH funding should also be allocated towards the development of an epidemiologic study on the incidence, prevalence, and severity of serious mental illness within the US.[144] The current prevalence of mental illness is estimated through the National Survey on Drug Use and Health administered yearly by the Substance Abuse and Mental Health Services Administration (SAMHSA), but it excludes a substantial portion of individuals without a fixed address, including individuals experiencing homelessness, military personnel on active duty, and individuals who reside in institutional group quarters, such as jails and hospitals.[145] The study is also cross-sectional, limiting the inferences that can be made on the incidence of disease, and how it is related to risk factors, such as genetic risk factors, traumatic experiences, and stressful life situations. A longitudinal study is necessary to fully investigate the causes and implications of serious mental illness over time. By more accurately describing the incidence and prevalence of serious mental illness, disease risk factors, and the health and societal impacts of disease and treatment (or lack thereof), we can better understand and quantify the needs of those living with serious mental illness and develop novel treatments to address those needs.

NIH BRAIN Initiative

The BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative, coordinated through the NIH, is the largest neuroscience project in history. It aims to develop new tools and technologies to understand and manipulate circuits in the brain.[146] On top of the annual NIH BRAIN Initiative appropriation, the 21st Century Cures Act authorized $1.5 billion over 10 years (2016-2026) for the Initiative as part of the Innovation Fund of the Cures Act. In 2021, $550 million was appropriated for the Initiative, which included $100 million in Cures Act funds.

Now at the half-way point, the BRAIN Initiative has made substantial progress in accelerating our understanding of the brain, its makeup, and its processes. For example, research has advanced what we know about different cell types, and their roles in health and disease, further established

circuit diagrams, developed tools for monitoring neural activity, developed interventional tools that change neural circuit dynamics, and further developed fundamental conceptual knowledge of the brain and mental processes.[146]
Yet many questions remain unanswered, and the second phase of the initiative will focus on large transformative projects that lay the foundation for developing interventions for human brain disorders. Priorities for the BRAIN Initiative 2.0 include developing new technologies that will help researchers better understand the human brain and treat its disorders, and researching how dynamic patterns of neural activity are transformed into cognition, emotion, perception, and action in health and disease.[146]

BRAIN 2.0 initiatives are ambitious, requiring new technological and scientific inventions, but if successful could provide the fundamental knowledge needed for treating brain disorders. Future funding opportunities for the BRAIN Initiate should be considered within the context of the tremendous amount of work that is needed to advance our understanding of the brain and the disease mechanisms for serious mental illness, as well as the work that is needed to facilitate the development of new treatments for serious mental illness.

Advanced Research Projects Agency for Health (ARPA-H)

In 2021, legislation was introduced to create an independent health agency that would be tasked with driving biomedical breakthroughs that provide transformative solutions for patients by promoting high-risk, high-reward capabilities or platforms. The Advanced Research Projects Agency for Health (ARPA-H) is inspired by the DARPA (Defense Advanced Research Projects Agency) program, an interagency effort to support and expedite innovative research projects that would likely not be successful in a traditional research setting.[147] While there has been speculation but limited detail on the eventual focus of ARPA-H, advocacy groups are working to promote the incorporation of neuroscience and mental health into the program, considering the higher risks inherent to CNS research.

The ARPA-H approach of supporting high-risk, high-reward research would be a much-needed shift within serious mental illness. APRA-H would be modeled after the "fast-fail" philosophy of DARPA-H, which is essential for quickly identifying negative results and avoiding future time-intensive and costly testing.

The Fast-Fail Trials Initiative

Analogous to the proposed ARPA-H framework, the NIMH previously funded three clinical trials through the Fast-Fail Trials (FAST) initiative to rapidly test, over a three-year period, new and repurposed medications for: (1) mood and anxiety disorders, including major depression and bipolar disorder (FAST-MAS), (2) psychotic spectrum disorders, including schizophrenia (FAST-PS), and (3) autism spectrum disorder (FAST-AS).[148] The goal of these trials was to identify targets in the brain that could facilitate future drug development, identify drugs that merited further testing, and eliminate drug targets with negative results from further testing.

The results of the three Fast-Fail trials were impressive. The FAST-MAS study demonstrated that a new compound had the hypothesized effect on brain circuits and established a proof of mechanism warranting further testing. The Fast-PS study allowed researchers to validate a biomarker of the effect of ketamine in the brain, which will facilitate further studies of this drug. And the FAST-PS study also identified a promising biomarker for future studies. [148, 149]

These studies demonstrate the promising potential for the fast-fail research framework within mental health, which could be continued through the ARPA-H program.

Clinical trial recruitment and retention

Clinical research participation can be challenging

for individuals living with serious mental illness due to the often disabling nature of illness, and researchers face barriers with recruiting and retaining participants in their trials.[136] Pharmaceutical companies and hospitals have implemented strategies to attract and retain participants, like payments for visits, coordinating study visits with other care visits, and conducting field visits to look for non-responsive participants. By using a combination of proactive efforts like these, one study was able to increase retention rates from less than 40% to 93% in the serious mental illness population.[150] The success of clinical trial retention strategies is relatively inconsistent, however, and the overall effectiveness of some strategies doesn't always translate from a specific clinical setting or population.[151] The positive effects of financial incentives, recruitment advertisements, and overall accessibility of clinical trial information have been shown, but have been difficult to translate on a larger scale. More work is needed to improve the engagement of patients living with serious mental illness in clinical trials in order to facilitate clinical research in this field. Moreover, ensuring diverse and inclusive representativeness in clinical research must be central to efforts to increase recruitment and retention of trial participants. As stakeholders consider barriers to participation, they should concurrently consider barriers that are preventing clinical trials from being representative of the populations they aim to treat in the real world.[152, 153]

Public-Private Partnerships

Accelerating Medicines Partnerships

The Accelerating Medicines Partnership (AMP) program is a public-private partnership between the NIH, FDA, and other public and private stakeholders, including patient advocacy organizations and pharmaceutical companies.[154] Since 2014, AMP programs have been launched in diseases that demonstrate a substantial need for new treatments, including Alzheimer's, Parkinson's disease, type 2 diabetes, and schizophrenia.[154] The goal of the AMP is to produce better treatments and diagnostic tools that can be used for AMP's focused disease areas. As previously discussed, drug development is timely and costly, and low success rates are often a deterrent to private investment within certain therapeutic areas. The AMP aims to mitigate the high risks associated with drug discovery by facilitating collaboration between AMP partners and NIH experts to select biomarkers that have the strongest potential for investigation within a specific disease area. By doing so, future research is more directed, increasing the chances of having a successful drug development outcome.

The AMP Schizophrenia (AMP SCZ) program was launched in 2020 as the first AMP initiative focused on a psychiatric disorder.[i] This biomarker discovery project is intended to identify and validate the most promising biological targets for therapeutics, define risk stages for schizophrenia, predict disease progression, and among other things, assess outcomes of individuals diagnosed with schizophrenia.[155] AMP SCZ is the single largest investment in mental health biomarkers that exists at NIMH. Knowledge gained from AMP SCZ will facilitate the initiation of proof-of-concept clinical trials to test hypotheses that emerge from the program.

Due to the success of the AMP SCZ program, there is stakeholder support for establishing AMP programs in other serious mental illnesses like bipolar disorder and major depressive disorder, where there is a similar need for biomarker and drug target research. As with schizophrenia, AMP programs for other serious mental illnesses have the potential to accelerate the process of identifying promising biological targets for drug development and improve the likelihood of successful clinical trials. Reducing failures in clinical trials can incentivize more companies to enter this space and bring new innovative drugs to market. Bringing these programs to fruition will require support from a range of partners and include funding commitments from both the NIH and industry.

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i The 5-year budget for AMP SCZ is $99.5 million, including $82.5 in NIH funding, $7.5 in industry funding, and $9.5 million in non-profit funding.

Case Study

Accelerator Program for Antibiotic Development

As with serious mental illness, innovation in antibiotics has not kept pace with medical need resulting from the rise of antimicrobial resistance worldwide. With few pharmaceutical companies investing in the development of new antibiotics to combat drug-resistant bacteria, the lack of new medicines to address emerging antibiotic resistance has become a global concern. The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) was launched to address this urgent need for greater investment in this area.

CARB-X demonstrates a unique model of public-private partnership between international governments and non-profits. Over 2016-2022, CARB-X is investing $480 million in research projects that have promise to develop life-saving products in antibiotic resistance.[156] Funding for CARB-X is provided from government research institutes in the US, UK, and Germany,[j] the Wellcome Trust in the UK, and the Bill & Melinda Gates Foundation in the US.

CARB-X is an impressive global effort in an area that has long needed therapeutic innovation. The model provides technical, business, and scientific support for projects through early phase clinical trials, so that promising products are more likely to gain support from pharmaceutical companies for clinical development. Applications for projects are accepted from around the world and are selected through a competitive process. Funding is restricted to products that will have large societal benefit by targeting high priority drug-resistant bacteria. CARB-X serves as a translatable model for how an accelerator program for serious mental illness could help mobilize global funding partners to advance the science needed to drive development of innovative treatments in this space.

j U.S. Biomedical Advanced Research and Development Authority in the U.S. Department of Health and Human Services, the UK's Department of Health and Social Care's Global Antimicrobial Resistance Innovation Fund, and Germany's Federal Ministry of Education and Research, with in-kind support from the NIH.

Regulatory Reform

Market Exclusivity Reform

As described in Section IV, the existing market protection periods are disadvantageous to pharmaceutical companies in serious mental illness, given the longer research times and ultimately higher costs.[130, 131] Regulatory reform has previously aimed to incentivize the production of drugs with significant unmet need, including orphan drugs and antibiotics, and similar programs are needed for drugs for serious mental illness and other areas of psychiatric drug development. While regulatory reform will not be enough to fully incentivize pharmaceutical company investment in psychiatric drug development, it should be one part of the solution. Regulatory reform to modify the market exclusivity terms for serious mental illness can help to ensure that as the science is developed to lay the groundwork for psychiatric drug development, companies are incentivized to start and continue investing in the area.

The Orphan Drug Act of 1983 created an incentive to develop drugs for rare diseases with less than 200,000 affected individuals.[157] Very few drugs were being produced for rare diseases at the time; in response, the Orphan Drug Act provided 7 years of market exclusivity post-FDA approval (in place of the existing 5 year exclusivity period for non-orphan drugs) to ensure that the investment in developing a drug in a rare disease was adequately rewarded. The Act also provides tax credits and access to government grants and technical advice from the FDA.[158] Since its implementation, it has been a successful means of ensuring therapies in rare disease come to market. Developing a similar reward for the development of drugs in serious mental illness could increase the initiation of new clinical trials.[159]

More recently, the GAIN (Generating Antibiotic Incentives Now) Act was established in 2012 to ignite interest in the development of new antibiotics. The GAIN Act provided an additional 5 years of exclusivity to manufacturers of novel

therapies on top of the Hatch-Waxman's baseline 5-year protection or the orphan drug 7-year protection. To date, the GAIN Act has not been as successful as the Orphan Drug Act in bringing innovative products to market, partly because the GAIN eligibility criteria were too broad, and the act was not constructed to properly identify drugs that would truly target an unmet need.[35, 160]

It has been proposed, however, that an adaptation of the GAIN Act could be successful for incentivizing pharmaceutical companies to increase their investment in drugs for serious mental illness and other CNS therapeutic areas.[35] On a case-by-case basis, drug candidates could be evaluated for additional market exclusivity, ensuring that only truly novel and innovative therapies, (as judged by outside clinician, research and patient experts), are granted the benefits.[35] This extended exclusivity period could: (1) attach to existing market protection(s) for which the drug is eligible, as in the GAIN Act or (2) supersede other protections, modeled off the orphan drug exclusivity period. In either event, based on experience garnered with the GAIN Act, this period would need to be sufficiently long to account for the high risk associated with drug development in this area.[35]

Adaptive Licensing

As described in Section IV, accelerated approval is a pathway which allows for conditional drug approval based on large studies demonstrating improvement in surrogate or intermediate endpoints of disease. This approval is granted by the FDA with a concomitant requirement that the drug manufacturer then conducts confirmatory studies that demonstrate improvement in the clinical endpoint. This pathway allows patients with high unmet need to access treatment earlier than would be expected under the traditional approval process which requires evidence of improvement in the long-term clinical endpoint. However, because there currently are no surrogate or intermediate endpoints in serious mental illness, the accelerated approval pathway cannot be utilized.

Proposed alternatives to accelerated approval may include adaptive licensing pathways. With adaptive licensing, the regulatory process would allow for conditional approval of drugs based on smaller studies of clinical endpoints. These smaller studies would focus on subpopulations of patients, for example those with high unmet need or who previously exhibited exceptional response to treatment. Smaller studies inherently provide greater uncertainty in results compared to the large confirmatory studies that are typically conducted before FDA approval. Following the conditional approval using smaller studies, clinical studies and/or analyses of real-world data would continue, and approval could be expanded or rolled-back given emerging evidence on the drug's efficacy and safety.[161]

The evidentiary standards for approval under adaptive licensing remain the same as with traditional approval, in that the demonstrated benefits of the drug must outweigh the risks. The difference is that there is a greater acceptance of the uncertainty of those benefits and risks given that decisions to approve a product are made based on data from earlier stages of clinical research, before large confirmatory trials are conducted. The risk tolerance of decision makers would be an influential yet subjective part of this approval process. Recent developments in Patient-Focused Drug Development at the FDA have allowed patients to provide input on the level of uncertainty that they are willing to accept to gain access to a new drug.

For patients living with serious conditions without effective therapies, for example those with rare diseases, patient communities have demonstrated tolerance for uncertainty regarding the risks and benefits of much needed therapeutics. [162] However, the use of drugs during these initial approval periods would require careful discussions between physicians and patients, including input from caregivers, about what is known and unknown about the risk and benefits of drugs.

Using an adaptive licensing pathway could make investments in certain therapeutic areas, including serious mental illness, less risky, potentially making the expected financial reward enough that it covers the investment in the clinical development and conditional approval processes.

It would also allow patients to benefit from greater access to drugs, with the important caveats that patients, and as relevant, caregivers, understand the level of evidence that is available for the drug and make informed choices in consultation with clinicians.

FDA Neuroscience Center of Excellence

In the last 5 years, there have been efforts within the FDA to streamline the medical product review process. These are initiatives needed across all therapeutic areas, but particularly for CNS classes of drugs which take on average 38% longer to advance through the approval process compared with non-CNS drugs.[131] Aiming to build upon these efforts, patient advocacy groups and other stakeholders have advocated for the establishment of an Intercenter Institute, also known as a Center of Excellence, focused on neuroscience at the FDA, emphasizing the need for enhanced collaboration between the FDA and external stakeholders to bring CNS treatments to market faster and in a more coordinated fashion.[163] At its core, the Neuroscience Center of Excellence (NCOE) would consolidate neuroscience expertise within the FDA and create processes to expedite the review and approval of CNS drugs, including those for serious mental illness, and enhance collaboration between researchers, clinicians, academia, advocacy groups, and industry in order to drive innovation in CNS therapies and devices.[164]

Oncology Center of Excellence

The first center of excellence established at the FDA was the Oncology Center of Excellence (OCE), which aims to accelerate cancer research and drug development. Since its founding, the OCE has been tremendously successful, and has initiated several programs that have helped to support and incentivize increased investment in oncology research. In 2018 alone, the OCE approved 35 fast-tracked therapies, 25 breakthrough therapies, and 18 breakthrough devices.[165]

The success of the OCE can serve as a model for the NCOE in moving products to market in an area with high unmet medical need. As new drugs and other technologies emerge for patients living with serious mental illness, the NCOE is urgently needed to expedite review of potential therapies and diagnostics.

Policies to Address Health System Barriers

In this section we: (1) identify initiatives that can work towards improving the mental health care system, which ultimately can improve the number of patients who receive treatment for their serious mental illness, and (2) discuss potential benefits to Medicaid payment reform.

Coordination of federal agency efforts on serious mental illness

The Interdepartmental Serious Mental Illness Coordinating Committee (ISMICC), was established through the 21st Century Cures Act in 2017 to make recommendations for actions that federal departments can take to better coordinate the administration of mental health services for adults living with a serious mental illness or children living with a serious emotional disturbance.[166] The ISMICC's membership includes representatives from key federal departments and agencies and non-federal public members.[166]

At its inception, the committee identified five goals for programming to better support those with serious mental illness: (1) creating a more organized and responsive federal system, (2) increasing accessibility to good care, (3) identifying and developing more effective options for treatment, (4) providing support for those living with serious mental illness in the justice system, and (5) encouraging more affordable solutions for serious mental illness treatment and care.[167] Specific policy suggestions from ISMICC have included improving education within the healthcare sector to better support patients living with serious mental illness, organizing and prioritizing next steps for serious mental illness research, and promoting earlier detection of serious mental illness in younger populations.

As the ISMICC approaches its statutory sunset in 2023, some stakeholders note that the committee has not realized its potential, attributed in part to low funding and a limited timeline. While ISMICC may not have met its original goals during the current authorization period, it could be more effective if it is reauthorized with greater funding. Notably, similarly situated interagency committees within other disease areas have proven successful and could serve as a model for ISMICC. For example, the DMICC (Diabetes Mellitus Interagency Coordinating Committee), established in 1974, has helped to catalyze new research projects, advocate for priority research areas within diabetes, and facilitate the collection of incidence and prevalence data.[168]

It is possible for ISMICC to achieve similar success in providing strategic interagency direction moving forward, provided it has adequate funding, dedicated leadership from within the government, and sustained engagement within both the public and private sector.

Mental health workforce

As previously discussed, the shortage of mental health professionals in the US is a significant barrier to patients accessing treatment—including innovative pharmaceuticals—for serious mental illness. One of the reasons that there are relatively few mental health care workers in the US is because salaries in this field lag behind others. Psychiatry, while being one of the most frequently recruited jobs within the medical field due to high and increasing patient demand, has lower salaries compared to other medical specialties.[169] Reducing loans for mental health professionals could help to increase engagement by making mental health professions more economically competitive.

Recent legislative proposals have advocated for increased loan repayment programming for mental health care workers, including the Mental Health Professionals Workforce Shortage Repayment Act, which would pay up to $250,000 in loans for mental health care professionals who work in underserved areas, and one sixth of an individual's eligible loans for each year of service.[36] This program would expand upon the policies already in place, which include Loan Repayment Program at the National Health Service Corps, which offer primary care medical, dental and mental health professionals up to $100,000 of loan repayment when signing a three year contract at a NHSC approved location.[170]

The expansion of loan repayment programs could be particularly beneficial for improving access to care for individuals with public insurance like Medicaid, who make up a significant portion of the serious mental illness patient population.

Mental health professionals often work in settings that serve patients with private insurance, due to higher reimbursement rates compared to public insurance. Loan repayment for practitioners that work in publicly funded community health practices can be one way to incentivize a more even distribution of care for individuals living with serious

mental illness, and greater access to the treatment regimens that that are essential to their health and overall functioning.

Insurance Coverage

Because a large proportion of patients living with serious mental illness are covered by Medicaid, the relatively low net reimbursement realized by manufacturers under this public program potentially limits expected revenue for new drugs and may be a disincentive to investment in this space.

Changes to Medicaid could be used to better incentivize research and development efforts for therapeutics that address high unmet need among Medicaid beneficiaries, including medications for serious mental illness.

As a prior example of how reimbursement policies can incentivize research and development efforts, when Medicare Part D was implemented, there was a substantial increase in Medicare reimbursement for prescription drugs. In addition, drug coverage for dual-eligible beneficiaries shifted from Medicaid to Medicare, which has higher reimbursement rates.[32] In the years that followed, research and development investment increased meaningfully for conditions that primarily impact the elderly.[32] Research and development also increased substantially for conditions that largely impact dual-eligible beneficiaries, including serious mental illness.[32]

Future studies that examine whether Medicaid reimbursement rates adequately reflect the value of therapies in serious mental illness may help to inform whether Medicaid payment reform is justified to increase innovation for drugs in high demand by Medicaid beneficiaries.

VI. Scientific Spillovers

Investment in developing treatments for patients living with serious mental illness can also improve patient outcomes in other disease areas. An example of this is in neurodegenerative disorders (NDD), where neuropsychiatric symptoms are common, and better treatment options are needed to improve the quality of life for NDD patients.

Patients living with neurodegenerative disorders, for example Alzheimer's disease (AD), other dementias, and Parkinson's disease, often experience neuropsychiatric symptoms.

Common neuropsychiatric symptoms for patients living with NDD include apathy, depression, hallucinations, and psychosis.[171] Up to 97% of dementia patients can experience neuropsychiatric symptoms, including depression (77%), anxiety (62%), hallucinations (18%), and delusions (36%).[172, 173] Around 18% of patients living with dementia will hallucinate and 36% of patients will have delusions.[173]

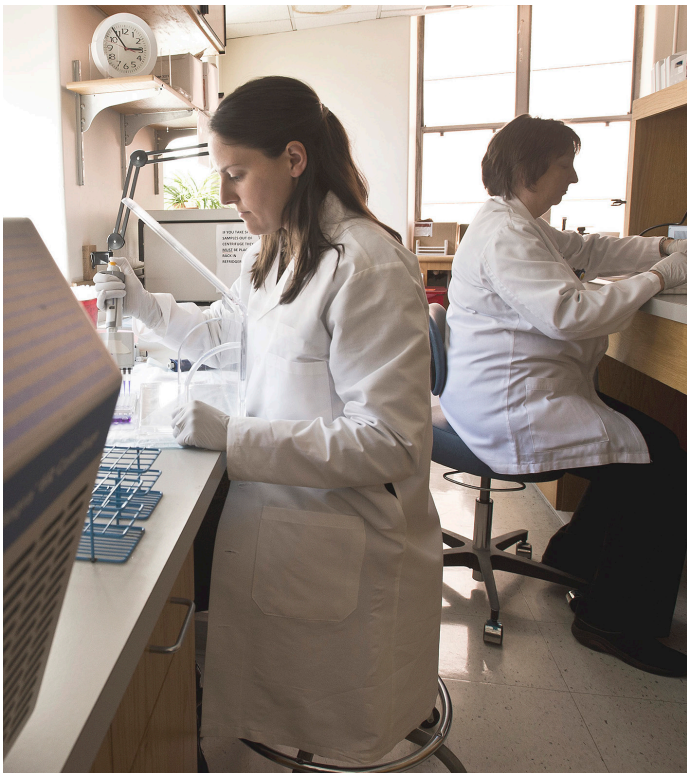
Neuropsychiatric symptoms can have significant impacts on the lives of patients living with NDD and their caregivers. Dementia patients living with neuropsychiatric symptoms experience greater health and economic burdens compared to dementia patients without neuropsychiatric symptoms. These burdens include increased direct care costs, which can exceed $10,000 per year, and increased caregiver burden.[173] Neuropsychiatric symptoms have also been linked to increased disease progression, with depression being a predictive factor for disease progression in Alzheimer's disease.[174]

Treatment options for patients living with NDD and neuropsychiatric symptoms are limited, and increased investment in treatments for serious mental illness may help these individuals living with NDD.

Over 60% of patients living with dementia take pharmaceuticals to alleviate neuropsychiatric symptoms.[175] Many general antipsychotic treatments have been used to reduce dementia specific psychosis and SSRIs have been used to alleviate symptoms of depression for patients living with AD.[173] However, while drugs can be beneficial in reducing symptoms, current treatments, especially antipsychotic drugs, have been found to increase mortality in dementia patients, and therefore are cautioned against overuse in patients living with dementia specifically.[173] As a result, there is an important need for new treatments in this area, and future research aimed at improving the lives of individuals living with serious mental illness will also help those with other disorders such as NDD that cause neuropsychiatric symptoms.

VII. Conclusion

To create more opportunity for innovations in serious mental illness, we need a deeper and more comprehensive understanding of the brain, its biomarkers, and its pathways. Government funding for basic science research should be complemented with public-private partnerships like the AMP programs that coordinate industry, academia, and government agencies to facilitate drug development. Examples of the historical successes of these types of collaborative efforts are promising and can likely be translated to benefit people living with serious mental illnesses, their caregivers and society overall. In addition to funding incentives, policymakers should consider regulatory reform, including the creation of exclusivity protections that reflect the specific and unique challenges of psychiatric research. Finally, health system and reimbursement factors that may pose barriers to innovation should be examined in light of the tremendous impact that serious mental illness has on patients and their families.



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