Three strategies to de-risk novel CNS therapies confidently

Development of therapies for CNS diseases has lagged behind other areas despite a growing global need for novel therapies. Because of the difficulty in developing and commercializing new treatments, many large biopharmaceutical companies have downsized and re-strategized their early-stage CNS drug development efforts. At the same time, advances in genomics and advanced imaging techniques have identified new targets that create the possibility of developing new antidepressants, antipsychotics and anti-anxiety drugs with novel mechanisms of action. Based on ongoing practices, we outline key strategies to consider for reducing the risk of drug development for CNS treatments.

Authors:
Larry Ereshefsky, Pharm.D. F.C.C.P. B.C.C.P.
Rebecca Evans, M.D.
Rohit Sood, M.D., Ph.D.
Doug Williamson, M.B.ChB., M.R.C.Psych.
Brett A. English, Pharm.D., Ph.D.
INTRODUCTION

More than 1 billion people worldwide suffer from diseases of the central nervous system (CNS).\(^1\) One in five Americans currently takes at least one psychiatric drug and mental disorders are recognized worldwide.\(^2\) In the United States and European Union the economic burden of CNS diseases—including direct medical costs, direct nonmedical costs, and costs of informal (family) care—is estimated at more than $2 trillion, a number expected to triple to $6 trillion by 2030.\(^3\) In 2010, the CNS therapeutic market was valued $78 billion, making it the second largest therapeutic category after cardiovascular.\(^4\)

Development of therapies for CNS diseases has lagged behind that for other therapeutic areas. CNS drugs can take more than 20 months longer to develop than other drugs and are less than half as likely to reach the market.\(^5\) While many CNS diseases fall in the orphan and rare disorders category, diseases such as Alzheimer’s are common, and a novel Alzheimer’s disease medication has the potential to reach blockbuster status.

Numerous trials for Alzheimer’s disease, major depression, stroke, and schizophrenia have failed—many in the costly Phase III stage of clinical development.\(^6,7,8,9\) In addition, much CNS drug development occurs at the same time that knowledge in the field is advancing—but unfortunately, clinical development programs cannot utilize those advances after the fact.
GLOBAL BURDEN OF CNS DISEASE\textsuperscript{1,3,11}

- Brain disorders are the leading contributors to the global disease burden, according to the World Health Organization (WHO), with depressive disorders as the single largest source of lost disability-adjusted life years in high-income countries and the third largest worldwide.

- In Europe, 38 percent of the population is said to be affected by brain disorders annually. In 2010 that burden was estimated at almost 800 billion euros.

- In the United States the fastest-growing threats to US health are diseases of old age including dementia, Alzheimer’s, stroke, Parkinson’s, and progressive hearing loss.

- Dementia incidence outpaces all other disorders. In the US alone, the economic burden of dementia is 12 times that of cancer.

The global pharmaceutical industry has significantly decreased its investment in treatments for depression, bipolar disorder, schizophrenia, and other psychiatric disorders.\textsuperscript{10} Large biopharmaceutical companies have restrategized their CNS research and development (R&D) efforts. Many companies have internally downsized and “de-risked” early-stage CNS drug development by shifting their activities to partnerships with emerging biopharmaceutical companies and academia, and increasing in-licensing and mergers and acquisitions (M&A) activity. Internally, strategies have been created to mitigate failures at earlier stages of drug development.
Many recent CNS R&D drug losses have occurred in the costly Phase III stage of clinical development. Reasons for failures include:

- Wrong dose or too low of a dose to hit the therapeutic target or inadequate brain penetration
- Heterogeneity of CNS disorders make it difficult to demonstrate a drug’s effect on clinical endpoints
- High placebo effect (in 30 to 60 percent of patients in some CNS indications)
- High patient dropout rates (again, in some but not all indications)
- Traditional preclinical disease models that fail to accurately inform the potential efficacy of compounds transitioning into Phase I/II, especially those with novel mechanisms of action
- Changing or unestablished regulatory requirements
- Incomplete understanding of the mechanisms that underlie brain disease and the regional circuitry that underlies complex behavior and cognition that underlies complex behavior and cognition

**Placebo Response Observed in CNS Disorders**

<table>
<thead>
<tr>
<th>Examples</th>
<th>Placebo-response (%)</th>
</tr>
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<tbody>
<tr>
<td>Major Depression</td>
<td>up to 60</td>
</tr>
<tr>
<td>Anxiety Disorders</td>
<td>up to 60</td>
</tr>
<tr>
<td>Parkinson’s Disease (Motoric Symptoms)</td>
<td>up to 50</td>
</tr>
<tr>
<td>Pain</td>
<td>up to 50</td>
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</tbody>
</table>

For example, the clinical trials conducted on a humanized anti-amyloid-beta monoclonal antibody for mild-to-moderate Alzheimer’s, was estimated to cost several hundred million dollars. One criticism of this program was that the standard Phase II study was skipped and the Phase III study was started based on biomarker data and not on signals of clinical efficacy. However, this study took place at a time when much less was known about the trajectory of amyloid deposition and the sequence of pathologic changes in AD.9

COULD THE REDESIGN OF EARLY-PHASE STROKE TRIALS IMPROVE SUCCESS?

Stroke is one of the leading causes of mortality and disability, but pharmacological treatments have made little progress in providing clinical benefit. The number of Phase III trials that have failed, particularly those oriented towards neuroprotection, is critically high. Consequently, pharma companies have shied away from investing in this field, and progress in the study of new and more effective therapies has been slowed. It has been suggested that the primary reasons for stroke trial failures are the design and endpoints of clinical studies, but, the translational animal models that have been used have also been criticized. A major contributor to the failure rate in Phase III has been that Phase II programs have provided misleading or suboptimal data for go/no-go decisions.12

<table>
<thead>
<tr>
<th>Develop. program</th>
<th>Number neg. failed studies</th>
<th>Number of Randomized Controlled Trial</th>
<th>Neg. /failed studies (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>50</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>3</td>
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<td>8</td>
<td>3</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>50</td>
<td>46</td>
</tr>
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</table>

The very nature of CNS diseases makes them challenging for drug development. Outcome measures in preclinical animal models have been largely observational and often conducted with no or inadequate blinding. Clinical trial outcome measures have generally relied on patients’ self-reporting or subjective clinical testing.

Many animal models do not accurately represent the human disease under study and, therefore, are not reliable in predicting the effects of novel therapeutics. In 2007 *The Scientist* published “The Trouble with Animal Models,” a report highlighting the failure of a highly anticipated neuroprotective agent for stroke patients. Metabolic, anatomic, and cellular differences between murine and human models were cited as contributors to clinical failures.

While the discovery of specific genetic mutations and creation of transgenic mice has facilitated the study of therapeutics for a number of indications such as ALS, the etiology of many CNS disorders remains elusive, and animal models continue to represent these heterogeneous diseases inadequately.

The CNS space is not lacking for new targets or mechanisms of action of drugs. Human genomics and the use of advanced imaging techniques such as fMRI regularly identify novel targets, creating the possibility of developing novel therapeutics with new mechanisms of action. Back-translating these targets to animal models is slow and complicated, and what targets will be the most successful remains to be determined.

Regulatory approval continues to be a great challenge. An April 2013 report coauthored by the Manhattan Institute and the Tufts Center for the Study of Drug Development found the FDA’s neurology review division (Division of Neurology Products) was among the slowest reviewers of medications, taking 635 days on average to review drugs and taking on average 1.73 review cycles to reach an approval decision. The division was cited as being the worst at meeting Prescription Drug User Fee Act deadlines. In 2014 the Manhattan Institute cited the FDA’s Division of Psychiatry Products as being among the top three worst-performing divisions. In contrast, the two fastest units of the FDA, Oncology and Antiviral, took under 200 days to review drugs.
In addition, the regulatory process around the world is in a constant state of evolution, and the requirements to show efficacy in certain disease states have changed. For example, over the past 20 years, the endpoints for the successful treatment of addiction have shifted from complete abstinence to harm reduction, an evolution that has developed more rapidly in the EU than in the US.

While there are many problems in CNS drug development, drug development for specific CNS diseases remains a worthwhile and enticing goal for companies. Mental disorders are not only common worldwide, but also increasingly recognized by healthcare systems. With CNS diseases afflicting millions and few therapies available, there is a vast unmet medical need. Many individuals with mental disorders remain symptomatic and often disabled despite existing treatments. Any drug that reaches the clinic has the potential to deliver blockbuster returns. Several clinical strategies may facilitate CNS drug development.
THREE STRATEGIES THAT MAY HELP DE-RISK CNS DRUG DEVELOPMENT

To avoid expensive, late-stage failures, biopharmaceutical companies should consider applying multidisciplinary solutions earlier in the development process. What follows are three strategies proposed to reduce failures and accelerate CNS drug development.

**STRATEGY 1**

Leverage the benefits of adaptive trial designs in both early and later clinical trial phases

Adaptive trial designs allow biopharmaceutical companies to plan modifications based on the data that accumulate during a study. Today, 20 percent of pharmaceutical trials are designed adaptively.\(^\text{16}\)

<table>
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<tr>
<th>ADAPTIVE TRIALS:</th>
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<tbody>
<tr>
<td>Use preplanned adaptations to correct initial incorrect assumptions</td>
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<tr>
<td>Enhance the efficiency of drug development by reducing the need to repeat trials that narrowly miss a clinical endpoint</td>
</tr>
<tr>
<td>Can eliminate unnecessary patient recruitment for overpowered designs</td>
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</table>

In early phase trials, variability in biomarkers and the magnitude of relevant drug effects (e.g., utilizing measures of Tau and Amyloid beta-protein 1-42 to assess the effects of BACE inhibitors) can be analyzed to guide the direction and magnitude of dose escalation, along with reestimating the sample size of subsequent dose cohorts (including the ratio of placebo to drug-treated subjects).

Adaptive design strategies can help increase the probability of success early for later trials and can help a biopharmaceutical company obtain more information per dollar invested to support better go/no-go decision making.\(^\text{17}\) When conducted correctly, adaptive trials allow more doses to be tested in Phases I and II, which leads to a better understanding of the compound and its effects on patients in doses that are clinically relevant. That can lead to better decisions around the drug’s development and, for successful compounds, a better-designed Phase III trial.

There is also an ethical benefit to adaptive trials: fewer trial subjects may be enrolled or fewer subjects may be given doses of medications that are ineffective or potentially harmful and can be switched earlier to doses that provide therapeutic benefit.

A recent study published in *Innovations in Clinical Neuroscience*, demonstrated how adaptive designs can increase the efficiency of psychiatric drug development.\(^\text{18}\) The study employed a continuous reassessment of the estimated dose-response such that patients were randomized in a double-blind fashion into one of seven disease categories of the investigation drug, placebo, or active comparator. Because of the adaptive design strategy employed, only 202 patients were
needed to make the determination of futility. In contrast, according to the author, a conventional design would have required “enrollment of 450 patients and considerably more time and expense to reach the same conclusion.”

While adaptive design is used extensively in oncology and cardiovascular disease, it is still relatively new in CNS.

One concern around the implementation of adaptive design in CNS is the validity of data generated from a regulatory perspective. Questions include:

- What level of adaptation will be acceptable to regulatory agencies?

- What are the regulatory standards for the review and approval process of clinical data obtained from adaptive trials with different levels of modifications?

- Does the clinical trial become a different trial after making the modifications for addressing the study objectives of the originally planned trial?

To address these concerns the FDA encourages earlier and more extensive interactions between the biopharmaceutical company and the regulatory agency. Companies are urged to seek FDA feedback on specific issues that may arise during the course of the trial.

Adaptive trial design requires advanced planning during the protocol development stage. The primary benefit of adaptive design is greater confidence that trial results have addressed the relevant issues and that those specific trial results lead to a clearer go/no-go decision. For instance, Phase II results often are inclusive, based on differential dropout in one arm or inadequate dosing to reach desired PK levels. By utilizing adaptive design measures biopharmaceutical companies can ultimately spend less time on unsuccessful compounds and can more quickly reassign resources to other drugs in their portfolios.19

The most common adaptive designs and their benefits are well documented and include:

- Stopping a trial early (or late—that is, extending accrual) with a conclusion of either superiority, noninferiority, or futility

- Optimizing dosing

- Dropping arms or doses and finding the best performing arms

- Combining Phase I/II and Phase II/III trials to save time and money

- Changing randomization proportions

- Finding the best population for a compound

- Reducing sample size per group or per direction of dose ranging

- Modifying wrong assumptions for effect size or population variance for an outcome measure

- An ethnic cohort to facilitate trial expansion into Asia, for example (inclusion of ethnobridging)

- Functional imaging to measure the compound’s effect on the brain (target engagement, receptor occupancy, dose-finding) and for planning the use of imaging techniques in later trials as biomarkers.
Invest in learning more from Phase I/IIA

Lack of efficacy is the primary reason for failure of new chemical entities.

In drug development Phase I/IIa has always served as a learning phase and Phase IIb/III served to confirm learnings gained. Precision medicine approaches utilize this same staged framework, but include more homogenous cohorts, and focus on the use of biomarkers to determine the safety and pharmacokinetics of a compound earlier in the development process.

To determine the likelihood that a drug candidate’s success will survive Phase II trials and improve its likelihood to progress to Phase III, drug developers are seeking to determine an integrated understanding of:

- **1** Exposure at the target site of action over a desired period of time (pharmacokinetic/pharmacodynamic principles)
- **2** Binding to the pharmacological target as expected for the drug’s mode of action
- **3** Expression of pharmacological activity commensurate with demonstrated target exposure and binding

Based on a study that reviewed 44 drug development programs at a Top 5 pharmaceutical company, this so-called “three pillars” approach focuses on dose-response evaluation and uses imaging and other biomarkers to measure pharmacological activity. This approach facilitates making a no-go decision earlier in the process if the wrong target is selected at the start of a program.

Success rates using this approach have been demonstrated in fourteen studies as follows:

- **Zero pillars met.** When none of the three pillars was met, not one compound achieved proof of concept (PoC).
- **All pillars met.** When all three pillars were met, fourteen of the drugs tested the hypothesized mechanism of action, twelve demonstrated proof of concept, and eight reached Phase III.

To some degree, this three pillars strategy has been adopted by almost all CNS companies. For example, the use of PET/CSF for exposure and binding and biomarkers for expression of effect has become common. More widespread adoption by pharmaceutical companies developing CNS therapies could improve the compounds that move forward in clinical development and help prevent later-stage failures.

As with adaptive trial designs, spending more time to design Phase I/IIa trials that allow PK/PD learnings require more upfront planning and investment, particularly regarding the data that will be collected and how that data will be analyzed.
Three Pillars of Survival for 44 Drug Development Programs at a Top 5 Pharmaceutical Company Between 2005-2009

- **Pillar 1 & 2**
  - Total = 12
  - 5 tested mechanism
  - 2 Phase III starts

- **Pillar 1, 2, 3**
  - Total = 14
  - All 14 tested mechanism
  - 12 tested mechanism & achieved positive POC
  - 8 advanced to Phase III

- **None or Partial Pillars**
  - Total = 12
  - 12 failed to test mechanism and all were Phase II RIPs

- **Pillar 2 & 3**
  - Total = 6
  - 5 tested mechanism
  - No Phase III starts

As part of its 2008 Strategic Plan, the US National Institute of Mental Health developed its Research Domain Criteria (RDoC) initiative to “create a new kind of taxonomy for mental disorders by bringing the power of modern research approaches in genetics, neuroscience and behavioral science to the problem of mental illness.”

The RDoC rests on three assumptions:

1. Mental illnesses are brain circuit disorders.
2. Neural circuit dysfunctions can be identified using the tools of neuroscience including electrophysiology, functional neuroimaging, and methods for quantifying connectivity.
3. Data from genetics and clinical neuroscience will yield biosignatures to augment diagnosis and identify symptom management protocols.

Though developed initially for psychiatry, the RDoC approach also lends itself to neurology. It begins with current understandings of behavior-brain relationships and links them to clinical phenomena instead of starting with the definition of an illness and seeking its neurobiological underpinnings. In other words, RDoC translates diagnoses into meaningful sets of symptoms or domains/subdomains that have a neurocircuitry basis. This framework is intended to guide classification of patients for research studies and to demonstrate that a drug is effective on one or more domains of symptoms (not a syndrome) to validate new targets.

Take a neurocircuitry approach inspired by the Research Domain Criteria (RDoC)

A SHIFT IN RESEARCH DEVELOPMENT AND DIAGNOSES?

Psychiatric disorders are the result of dysfunction in several domains of brain function such as cognition, motivation/reward, fear/anxiety.

Each domain and sub-domain, i.e., presenting symptom/measurable finding in people, is linked to brain circuitry networks,

- Dysfunction in a domain is reflected in circuitry, preclinical, and clinical models.
- Sets the stage for symptomatic (phenotypic) approval path provided there is scientific support, rather than use of a diagnostic system
  - Impaired cognition in multiple diagnoses, i.e., DA/COMT, D1, working memory
  - Anhedonia across Mood/Anxiety, i.e., Opioid, GLU, reward/motivation

RDoC assumes dysfunction in neural circuits can be measured by electrophysiology (QEEG, ERP, PSG), functional neuroimaging (fMRI, FDG-PET), neurocognitive/behavioral assessments, and methods for quantifying connectivity.

From an April 2015 presentation to the College of Psychiatric and Neurologic Pharmacists (Brett English and Larry Ereshefsky)
For CNS drug development, a neurocircuitry approach would allow biopharmaceutical companies to develop customized data packages based on drug pharmacology, precision medicine considerations, and functional circuitry that provide critical information to inform and de-risk a molecule. Go/no-go decisions could be made based on whether the molecule being studied not only engages the target in the traditional sense (e.g., binds to a receptor, inhibits an enzyme) but also affects the circuitry relevant to a behavioral or cognitive phenotype.

In early-phase and proof-of-concept studies, focus on neurocircuitry engagement relevant to a specific research domain is more important in making a go/no-go decision than whether it has significant effects on a behavioral clinical endpoint such as a psychiatric rating scale. Depending on preclinical and clinical neurocircuitry models, studies could use healthy volunteers to confirm that the neural circuitry of interest is engaged via drug pharmacology.

The RDoC framework has been applied in autism, mood and anxiety disorders, and psychotic episodes, among others. For example, in 2014, a researcher proposed a novel method of treating adolescent depression based on the RDoC.\(^{25}\) The program prioritized the core domains of function hypothesized to drive the pathophysiology of adolescent depression and employed straightforward and feasible treatment strategies selected based on current scientific evidence. Blom and her coauthors suggested specific neural circuits be targeted in their novel treatment model rather than full constructs, given that the adolescent brain is still developing.

While neurocircuitry approaches are relatively new, regulatory authorities have shown increased interest. Biopharmaceutical companies need to work closely with regulatory authorities to assure the data generated during such a trial can be used as the basis of market application.

**CONCLUSION**

Neurological disorders significantly outnumber diseases in other therapeutic areas, inflict higher treatment and loss of productivity costs than cancer, cardiovascular disease, and diabetes combined, and they are growing in incidence faster than any other disease class in the US and the EU.

We are at the beginning of an era when CNS drugs development requires both flexibility and creativity on the part of drug developers. To reduce the risks in CNS drug development, biopharmaceutical companies need to ensure that scientific hypotheses about a potential new drug are addressed in the best possible way from start to finish and leverage both current and cutting-edge tools to increase decision-making confidence in the early, less costly stages of clinical research. Strategies to reduce failures and accelerate CNS drug development include the use of adaptive trials, investing in learning more from Phase I/II studies, and taking an RDoC/neurocircuitry approach.

For those involved in CNS drug development, the opportunities are significant, and patients will be the ultimate winners.
ABOUT THE AUTHORS

Larry Ereshefsky, Pharm.D., F.C.C.P., B.C.C.P., serves as Vice President, Early Phase and Global Therapeutic Area Lead, CNS at PAREXEL. Larry is recognized as a leader in clinical translational CNS research and clinical trials methodologies for CNS, with expertise in development and use of biomarkers and novel technologies to enhance signal detection and to ensure appropriate patient population selection. He is utilized as a global resource within PAREXEL and has extensive experience working with regulatory agencies. Larry has published more than 130 peer-reviewed scholarly articles and abstracts, presents his research at peer-reviewed professional and scientific meetings of learned societies, and recently co-authored with S. Jhee, M. Yen, and S. Moran, the book “Accelerating Global Drug Development: The Science and Practice of Ethnobridging.” In addition, Larry has served twice on the FDA Psychopharmacological Drugs Advisory Committee and USP Psychiatry Special Panels. He currently serves on the FNIMH working group for CSF Biomarkers in Alzheimer’s disease.

Rebecca Evans, M.D., M.S., serves as Global Therapeutic Area Lead Neurology at PAREXEL. Rebecca has more than 20 years clinical and drug development experience in neurology and neurosciences and has worked in both pharmaceutical company and contract research organization (CRO) settings. Her drug development experience extends from Phase I through Phase IV in multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and stroke recovery. Rebecca has held faculty appointments at the University of Indiana and the University of Kansas. She was Principal Investigator in over 30 clinical trials, held multiple investigator grants, and authored over 50 peer-reviewed publications and abstracts.

Rohit Sood, M.D., Ph.D., serves as Medical Director and Head of Advanced Imaging at PAREXEL and has worked as medical lead on more than 60 imaging clinical trials ranging from early to late phase. Dr. Sood has worked on several Alzheimer’s (AD) clinical trials, helping sponsors develop criteria for evaluating the eligibility, efficacy and safety aspects of their studies. He has also helped sponsors apply the revised McDonald criteria to Multiple Sclerosis (MS) trials and identify exploratory endpoints using advanced MR methods. In addition, he has helped develop criteria for CNS safety assessments in oncology trials. Dr. Sood has published extensively in the CNS space in peer reviewed scientific journals and has presented at various CNS conferences.

Doug Williamson, M.B.ChB., M.R.C.Psych., serves as Vice President, Global Therapeutic Area Leadership at PAREXEL. Doug provides leadership and operations oversight in the delivery of medical expertise to clients and internal customers across all therapeutic areas and regions. Doug is an experienced and accomplished clinician and researcher with broad knowledge of both neuroscience and drug development with more than 20 years of academic and pharmaceutical industry research experience. Prior to joining PAREXEL, Doug headed the Early Phase Neuroscience Clinical Research group at Eli Lilly and Company, where he spent several years as head of the Cymbalta medical affairs group, and prior to that led successful registration programs for Zyprexa and Symbyax.

Brett A. English, Pharm.D., Ph.D., serves as Senior Director for Scientific Affairs, Specialized in Clinical Translational Neurosciences and Psychiatric Pharmacy at PAREXEL. Brett has more than 10 years experience as a clinical scientist and principal or co-principal investigator on a number of investigator-initiated and industry-sponsored areas, such as schizophrenia, major depression, bipolar disorder and PTSD. He served as vice chair of the Institutional Review Board (IRB) and as chair of the Scientific Review Committee at the VA Medical Center in Alabama. Brett has published more than 40 peer-reviewed scholarly articles, book chapters and abstracts and presents his research at peer-reviewed professional and scientific meetings at clinical and basic science meetings.
REFERENCES


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