

# The Death of CNS Drug Development: Overstatement or Omen?



Regrettably, the past year has been notable for several large pharmaceutical companies fundamentally abandoning or severely restricting their neuropsychiatric drug development efforts, citing costly and long drug development periods with disproportionately lower chances of successful central nervous system (CNS) drug applications. A recent report by the Tufts Center for the Study of Drug Development (Tufts CSDD)<sup>1</sup> suggests that as little as 8.2% of CNS drug candidates ever become available for clinical use, compared with 15% of other drugs. It also takes more time to get regulatory approval—approximately 1.9 years for CNS drugs, compared with an average of 1.2 years for all other non-CNS drugs. In addition, Phase II and III development for CNS drugs takes an average of 8.1 years, more than two years longer than development for drugs in other therapeutic areas. Some CNS drugs take as long as 18 years from preclinical work to marketing, leaving little to no patent protection. Importantly, trial failures in CNS tend to occur later in the clinical development process, when resource demands and costs are at their highest. In fact, it was estimated that only 46% of CNS candidates succeed in Phase III trials, compared with 66% on average for all other drugs, making the cost of developing a CNS drug among the highest of any therapeutic area. Given this data, the risks associated with CNS drug development are currently weighed as being too great for many pharmaceutical companies, regardless of the continued need for treatment and an ever burgeoning market for many CNS drugs.

Even before the publication of the Tufts CSDD report, the development of CNS drugs has long been known to be fraught with innumerable complexities and obstacles (both genuine and perceived) compared to other therapeutic areas. Some of the more salient obstacles include a general bias regarding psychiatric illness and drugs, as well as a number of special concerns associated with CNS development that need to be successfully addressed during the course of the development process. Despite the advent and acceptance of biological psychiatry and the abundance of awareness campaigns regarding mental health issues, many lay people, and even healthcare providers, still inaccurately view CNS disorders as somehow less important than “real” diseases. This attitude belittles the value of CNS treatments, which are often seen as disparate from more “physical” ailments.

This bias can be seen when relatively more infectious disease and oncology therapies are being tested and approved compared to CNS therapies, reportedly due to their inherent “risk-benefit profile”, in which more risks (such as the side-effects and negative health consequences of a drug) are tolerated if the drug is also proven to be therapeutically efficacious. For many CNS indications this risk-benefit ratio is skewed, so that only negligible or no risk is acceptable.

For example, many CNS drugs are metabolised by P450 3A4 or 2D6 pathways, which are common substrates for innumerable CNS and non-CNS concomitant medications, increasing the drug’s risk-to-benefit ratio via potential drug-drug interactions and greater side-effect profiles. This low to no acceptable risk level seems to apply especially to disorders that appear to treat “lifestyle”-type ailments such as depression, anxiety, and attention deficit disorder, which the general public (and even some healthcare providers) often misperceive as only impacting a person’s temperament and quality of life, while having little to no effect on their overall health. However, it is well known that the risks of not treating mood disorders include increased morbidity and mortality from related medical illnesses and suicide, as well as the worsening of other purely “physical” ailments due to stress interactions and treatment non-compliance<sup>2</sup>.

In fact, according to a global study by the World Health Organization (WHO), depression may well be the most disabling disease in the world, and people with chronic physical diseases such as angina, arthritis, asthma, and diabetes are far worse if they also suffer from depression<sup>3</sup>. Despite increasing and overwhelming evidence such as this, CNS disorders continue to be stigmatised. In one sense this bias can be inferred by the relative lack of press and general criticism following the announcements of several major pharmaceutical companies’ plan to abandon their CNS portfolios<sup>4</sup>. One cannot help speculating that if a similar renouncement occurred in areas such as cardiovascular (CV) disease, diabetes, or oncology, this would have been followed by a fierce uproar from patient advocacy groups, the general public, and the press.

Trial sample size has also been cited as another manifestation of bias in CNS drug development<sup>5</sup>. For example, as a rule CV trials are strikingly larger than psychiatric trials. While it would not be unusual to have 10,000 to 40,000 patients in a single CV study, most psychiatry studies have less than one-tenth that number (roughly 300-500 patients). Even the relatively large CNS trials sponsored by the National Institutes of Health (NIH) have no more than a few thousand patients each, resulting in a relative reduction in statistical power compared to CV trials. This may be an artifact of the pharmaceutical industry’s reluctance to invest in psychiatry trials, due not only to internal, methodological complexities but also to external pressures. The field of psychiatry is forced to deal with a strong and active “anti-psychiatry” movement made up of politicians, foundations, religious groups, and lay people who fundamentally do not believe in the benefits of psychiatric treatment. There appears to be no such interest groups for other disorders seen as purely “physical”.

The bias against CNS drug development also manifests itself in approval trends by regulatory agencies, in which certain drugs are “fast-tracked” for approval due to perceived medical importance, such as those that can potentially treat serious or life-threatening illnesses, or those that address an unmet medical need. Researchers have reported that oncology drugs have a disproportionately higher share of FDA priority review ratings, orphan drug designations at approval, and drugs granted inclusion in at least one of the FDA’s expedited access programmes<sup>6</sup>.

CNS drugs often start off in a relatively poorer position than drugs in other indications, not just because they are viewed as having a relatively higher risk and lower priority, but also because CNS drug developers are not routinely taking advantage of the regulatory tools available to them, such as Priority Review and Fast Track designation. There are innumerable CNS conditions that would be considered serious or life-threatening and therefore eligible for Fast Track designation. Given the lack of effective treatments, the growing number of treatment-refractory CNS patients, and the high degree of intolerable side-effects, many CNS development programmes would be considered to address an unmet medical need and be eligible for Fast Track designation.

The Fast Track designation enables early interaction with the FDA that can help to clarify elements of clinical study design whose deficiency or absence upon the submission of a new drug application (NDA) could delay approval decisions. Although the FDA makes similar interactions available to any sponsor who seeks consultation throughout the stages of drug development, these meetings are not always guaranteed. A unique option within the Fast Track designation is the opportunity to submit sections of an NDA to the FDA as they are ready, rather than the standard requirement to submit a complete application at one time. Thus, many CNS development programmes miss out on some of the essential advantages associated with this special designation. Regulators should encourage this approach and also endeavour to lower the regulatory “bar” for more traditional CNS programmes in cases where treatment need is greatest. This, as well as a simple extension of patent licences, could result in a major reduction in the apparent risk profile for many CNS compounds, and a subsequent increase in pharmaceutical investment in this area.

In addition to this bias there are existent intrinsic complexities in CNS drug development that have discouraged pharmaceutical and biotechnology companies. Although most companies enter into CNS development programmes fully aware of these complexities, they are often minimised or even ignored in favour of the potential payoff of a CNS drug approval, given the enormous and ever growing CNS customer base. In fact, the number of patients with CNS disorders far outstrips those with CV disorders. Given population trends in which those 85 years and older will quadruple by 2050, with accompanying increases in neurodegenerative disorders, this dominance is likely to intensify. The potential size of the untreated CNS markets is so great that the future growth of the global neuropharmaceutical market could outpace the growth in all other sectors of the pharmaceutical industry<sup>7</sup>.



Below are some of the more salient reasons that may make the design and conduct of CNS drug development programmes relatively more challenging and risky than other indications:

- The relative lack of knowledge of fundamental biology and pathophysiological underpinnings of many CNS disorders
- The relatively poor predictive validity of preclinical models, and lack of accepted biomarkers and surrogates by regulatory authorities and the scientific community
- The relatively high use of subjective investigator and patient-rated diagnostic scales and primary endpoints, ultimately resulting in heightened placebo response
- The relatively large number of failed trials (not just non-significant trials) in which an already approved active comparator fails to differentiate from placebo, resulting in more trials to secure two adequate and well-controlled studies
- The relatively lengthy and fluctuating treatment periods for chronic illnesses, resulting in tremendous variability in treatment response over time
- The relatively novel mechanisms of action for many CNS drugs that by definition are associated with a higher risk of failure

Arguably, all of these factors have made CNS drug development comparatively more challenging for drug developers, resulting in poor CNS pipelines. Paradoxically, in an effort to respond to diminishing pipelines, many companies may have prematurely or inappropriately progressed CNS drugs into the Phase IIb/III setting based on marginal efficacy, inappropriate subgroup findings, inefficient data analyses, and specious conclusions from prior studies (especially in terms of dose selection). It also appears that many drug development teams have failed to truly benefit from proof-of-concept (POC) studies. POC studies should not habitually be designed and powered as potential back-up registration trials as they often are, but rather should take the form of a precise innovative experiment that specifically addresses one or two major objectives in a rigorous manner and often in enriched patients — the

results of which would inform eventual registration studies. Instead, gathering information regarding dose selection, exposure-response, and the means and variances of the primary outcome measure should be the goal of POC trials. Companies should also take advantage of regulatory input at the end of Phase IIa to help interpret POC data when designing registration studies.

The rush to Phase III and functional “silo”fication of big pharma departments has also resulted in tactical processes that can be antithetical to the strategic goal of drug development. Many companies segregate functions based on drug phase utilising disjointed functional teams. Lessons learned from one phase or team are often lost in the handoffs, with each team having its own goals, preconceptions, and biases that can be fundamentally at odds with each other. Long gone are the days when a well-seasoned singular drug development team with a unified goal and sense of ownership, equipped with unique knowledge of the drug’s attributes and pitfalls, and led by an expert product development champion/clinician could successfully usher a drug along the entire drug development pathway. It can be argued that not only are much needed information and a sense of responsibility lost in the handoffs, but also any chances of fortuitous, impromptu and unplanned explorations.

A recent meeting of the American College of Neuropsychopharmacology (ACNP) has concluded that it still may be premature to search “deductively” for psychiatric medications, reminding us of the important role that serendipity has historically played in neuropsychiatric drug development<sup>8</sup>. It was also suggested at this meeting that investigators should be alert to and note promising observations rather than simply discard outliers, and that they should initially utilise small pilot studies on the drug of interest. Further support was given for an open, dose-ranging trial followed by a move to a small sample, randomised clinical trial, all well before the move to Phase III. Furthermore, co-development of neuropsychiatric drugs with publically funded research institutions was also recommended to help to reduce the inherent risk involved in the CNS development process.

Unfortunately, the large amount of information gleaned from recent basic science innovations has had very little clinical relevance and, despite newly acquired knowledge gained on an almost daily basis, the past few years of CNS drug development have been characterised by relative stagnation. No matter the explanation for the lack of advancement of CNS drugs (whether bias, trial complexity, difficulty in study conduct, or some combination of many factors), most drug developers agree that there is an immense opportunity for expansion in the CNS marketplace. This fact alone should make CNS development attractive to the pharmaceutical and biotech sectors. Reducing patient suffering, prolonging life, and responding to very important public health concerns all demand greater efficiency in the clinical trial process resulting in an improved ability to secure approval for CNS drugs in a more timely and cost-effective manner.

Some of the recommendations above — such as a return to a singular clinical development team that ushers a drug

through the entire development process in a manner that maximises the possibility of serendipity and learning from prior studies; an increased utilisation of Priority Review or Fast Track designation with an accompanying decrease in regulatory burden; an increase in co-development or risk-sharing with publically funded institutions and the creation of networks of development partners; and increased attentiveness to the far-reaching effects of stigmatisation of CNS drugs and disorders — should all aid our shared goal of getting safe and effective CNS drugs to those most afflicted.

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