Overcoming Regulatory Challenges in Cognitive Drug Development

In recent years, numerous pharmaceutical and biotechnology companies have undertaken development programmes intended to assess the efficacy of various pro-cognitive drugs on a wide variety of cognitive domains across several psychiatric and neurologic conditions. Findings from these studies have suggested that several putative cognitive enhancers have some limited efficacy across a wide variety of indications, including ADHD – (attention deficit and hyperactivity disorder), bipolar disorder, major depression, Parkinson's disease, PTSD – (posttraumatic stress disorder) and of course schizophrenia. Despite progress to date regarding the development of compounds intended to treat Cognitive Impairment Associated with Schizophrenia (CIAS) there is relatively little information available on how to determine the legitimacy of a given cognitive therapeutic target outside of schizophrenia. The following is an attempt to describe some of the more salient regulatory challenges involved in determining the appropriateness and legitimacy of a possible target involving cognitive impairment associated with various CNS – (central nervous system) disorders and how to overcome these challenges.

To date most CNS drugs have registered claims for a recognised specific disease or syndrome, and for the most part these claims tend to be focused on the disease entity rather than specific features of the disease. More recently, however, regulatory agencies have approved development programmes and several compounds for indications reflecting specific features of a disease such as negative symptoms, suicide ideation and cognitive impairment in schizophrenia; agitation in bipolar disorder and autism; impulsive aggression in ADHD; and even walking in multiple sclerosis. Given that these indications have been considered legitimate targets for drug developers, many drug developers have maintained that cognitive impairment associated with other CNS disorders would also represent a legitimate target. By way of example, this watch article will posit that a specific type of cognitive impairment known as Executive Dysfunction (ED) is a cardinal feature of both untreated and treated child and adult ADHD, and therefore would represent a legitimate target for drug developers.

The assumption is based upon a general consensus from a variety of cognitive, behavioural and imaging data, suggesting that a wide array of cognitive difficulties can be subsumed under the construct of ED, which has also been referred to as Executive Function Disorder, Dysexecutive Syndrome, Cognitive Dysexecutive Disorder, Prefrontal Executive Dysfunction, Fronto-Cortical Dysfunction, and Fronto-striatal Dysfunction, depending upon the indication with which it is associated. Given the myriad designations there initially needs to be agreed-upon terminology to characterise and denote ED in ADHD. This moniker should distinguish the uniqueness of ED as reflected in diagnostic nomenclature that signifies that this cognitive construct is different from any other constructs that regulatory bodies may be currently entertaining in ADHD or other disorders. It is important to note that ED is also a key symptom readily apparent in Parkinson's disease, Bipolar/Unipolar Depression, Traumatic Brain Injury, and Obsessive Compulsive Disorder, as well as in non-psychiatric disorders such as primary breast cancer. Thus, it is important to determine if the ED associated with ADHD manifests itself differently from other indications and importantly that this ED is a symptom of the ADHD and not simply a result of treatment. The presence of symptoms across the natural history of the indication is also important to establish, as ideally symptoms should be apparent in early untreated patients and be fairly constant and refractory to medications designed to treat symptoms of ADHD later in the disease.

Regardless of the exact terminology used, or even the indication under investigation, it is generally agreed that the underlying neurocognitive construct constituting ED is composed of difficulties across many of the following cognitive domains:

- Organisation and planning
- Working memory and self-monitoring
- Sustained attention / divided attention or vigilance / distractibility
- Impulsivity / behavioural inhibition
- Set shifting / cognitive inflexibility / perseverations
- Processing speed
- Initiation and fluency

These cognitive domains can be accurately measured by a number of validated and reliable neuropsychological and behavioural measures, suggesting that any changes associated with novel drug intervention can be measured effectively in a controlled clinical trial setting. As cognitive measures sample multiple areas simultaneously (for example, most tests will simultaneously examine divided attention, processing speed and visual reasoning) it is important to determine exactly how individual cognitive tests are assigned to their respective domains. It is unclear if a MATRICS-type (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative will be required to define these cognitive domains, their constituent parts and their relative contribution (weight) to the overall ED construct or how these should be best accomplished (e.g., via a Rand-type panel methodology, the consensus of a formal neurocognition committee, exploratory/confirmatory factor analysis or some combination of these). Once the agreed-upon cognitive construct of ED is firmly established, it is necessary to provide evidence that existing ADHD drug treatments do

not have a meaningful effect on ED; or that there is no meaningful treatment for a specific subtype of the ADHD characterised by a prominence of ED symptoms. It is possible to have a legitimate drug target and subsequent label, even if ED exists only in a small portion of patients. It can be argued that the cognitive impairment associated with ED in ADHD diminishes the response to ADHD medication such as psychostimulants and the overall treatment response. In either case the approved drugs for ADHD should not meaningfully treat the construct of ED.

Importantly, data establishing this non-response can help to provide evidence to regulatory agencies that the intended target is not pseudo-specific. The notion that a claim is pseudo-specific remains one of the single biggest hurdles to overcome in cognitive drug development. Pseudo-specificity is a term coined by Paul Leber and was first applied in connection with claims advanced for the use of benzodiazepines in anxious patients suffering from specific medical conditions (anxiety of heart disease, cancer, etc.)[1]. Leber opined that such claims were misleading because they sought to promote a distinction without meaning; consequently, these claims were rejected because they were held to be in violation of the requirement that a product's labelling not be false or misleading. As an example, Leber suggested that a claim that a marketed antibiotic is effective for the pneumonia of dementia even if based on empirical evidence is a pseudo-specific, because the linkage between pneumonia and the diagnosis of the patients treated is of no pharmacologic or biological importance, existing solely because of the sponsor's decision to select demented patients with pneumonia as subjects for study. By contrast, a legitimate disease-related claim requires a demonstration that the effect of the drug is in some way conditioned on the presence of the diagnosis (the diagnosis of the disease controls to what extent, if any, the effect of the drug is expressed)[1].

Another way to think of pseudo-specific claims is to consider them as artificially narrow claims. Some examples of such narrow claims centre around artificially narrow subgroups, symptoms or symptom clusters, or comorbid conditions, and examples of these which have been ruled on as pseudo-specific by regulatory agencies include depression in women, depression in the elderly, hallucinations in schizophrenia, depression in Parkinson's disease and dental pain[2]. A claim would be considered pseudo-specific or artificially narrow by focusing on a subgroup within the population of interest or on a particular aspect of the illness, such as a particular symptom in the absence of any empirical evidence to support such a restricted focus. As such, these claims serve only to permit a promotional advantage for the drug, since they imply an advantage of that drug over other drugs in the class for the symptom of interest[2]. Thus, regulatory agencies must be supplied with data suggesting that the treatment of ED in ADHD is not too narrow a disease-related claim, and therefore, not pseudo-specific.

There are several empirical approaches to overcome regulatory concerns that a claim is too narrow or pseudo-specific, and given these approaches, CNS drug developers should always approach any regulatory rejection of an initial claim as a straw man position that can be overcome with empirical data indicating the value of targeting the particular domain or subgroup[2]. Fortunately, CIAS serves as an example of a successful disease-related target within the schizophrenia syndrome, and as such is a target that can be utilised as a model to overcome regulatory concerns of pseudo-specificity in other CNS indications. Briefly, the claim for CIAS was established and legitimised based on several factors, including the fact that CIAS is a valid and well-known aspect of schizophrenia, that available treatments do not impact CIAS, and that the time course of CIAS is different from other important symptoms such as positive symptoms, and is present before the onset of positive symptoms and present in residual stage of illness[3]. Using similar arguments and methodologies, cognitive impairment associated with depression is now under consideration as a legitimate target for drug development.

Specifically, the methodological approaches to overcoming regulatory concerns regarding pseudo-specificity revolve around providing evidence that in residual phases of illness there is a persistence of symptoms; in this case ED persists despite broad ADHD treatment; or that that ADHD treatment is not beneficial for a distinct subtype or subgroup of patients who have ED. There are several experimental design options that are available to researchers that could potentially demonstrate the above assertions. Two of these designs involve patients in the residual phase of illness, and one design involves more acute patients[2].

The first of these designs is intended to demonstrate efficacy in an adjunctive study targeting ED in ADHD patients who are on stable doses of medication such as psychostimulants, but who are still experiencing ED. In this case, the novel drug under investigation would adjunctively treat only the ED and not overall ADHD symptoms such as hyperactivity. If the addition of the novel drug improves overall ADHD symptomatology, the drug would not meet the hurdle for a specific claim for ED and would be rejected based on the pseudo-specificity argument[2]. A recent example of this can be seen in Shire's lisdexamfetamine dimesylate augmentation study of persistent executive function in adults with partial or full remission of recurrent major depressive disorder, which reportedly improved executive function based on the Behavior Rating Inventory of Executive Function-Adult Version Global Executive Composite T-score (BRIEF-A GEC T); but also unfortunately improved symptoms on a measure of depression (MADRS), albeit mostly on items related to cognition4. As such, lisdexamfetamine dimesylate would at most be considered as an adjunctive antidepressant by regulatory authorities based on this trial, but would not meet the regulatory hurdle for a legitimate target claim of ED in depression.

The second of these designs involves a switching maneouvre in residual-phase ADHD patients showing continued benefit on ADHD symptoms but increased benefit (or decreased ED) when switching to a novel drug. Data from this study would need to demonstrate that the overall ADHD response remains adequate during the switch and that ADHD symptoms are maintained at similar levels[2]. However, cognition as measured by ED scales should improve when the subjects are switched to the novel drug. An essential problem with this type of switching design lies in regard to the interpretation of superiority as there is no placebo control. Without a placebo control it is unclear if the novel drug has true pro-cognitive effects and is increasing executive abilities; or if the novel drug simply impairs EF to a lesser degree than the comparator drug; or if the novel drug is neutral in terms of EF while the comparator drug is detrimental[2].

A third type of study design involves acute-phase patients comparing two drugs on the construct of ED, the novel drug and a comparator. This type of study would need to provide data that both drugs have effects on overall ADHD symptoms but only the novel drug would be superior to the comparator on ED. In this case, both drugs would need to be shown to positively impact overall ADHD symptoms by being superior to placebo on an ADHD scale measuring broad symptomatology[2]. However, it is important to note that claims of superiority in ED measures could potentially mean that the novel drug beats placebo only on ED measures while the active control does not beat placebo, or that the novel drug is also superior to the active comparator on ED measures. It is unclear at this point if regulatory bodies will insist on the latter requirement but this seems unlikely. Should superiority over the comparator be mandated this represents a very high hurdle for CNS drug developers[2].

Finally, regulatory agencies have differed on their view of the necessity of a functional co-primary for labelling pro-cognitive drugs. Researchers have long posited that improving cognitive dysfunction should lead to enhancing functional outcomes as cognitive deficits have been implicated as an impediment to gaining enhanced functional status, and a direct relationship has been demonstrated between cognitive impairment and poor functional outcomes for various patient groups such as schizophrenics[3]. However, this type of evidence may not be enough to satisfy issues regarding clinical meaningfulness, and US regulatory agencies have traditionally insisted on a functional co-primary or proxy in prior cognitive dysfunction programmes[2]. Many drug developers may simply view the mandate for a co-primary as a relic from the well-established Alzheimer's disease labelling requirements, but US regulatory bodies have suggested this as a way to overcome any concerns regarding clinical relevance of any small benefits that might be seen on cognition and thus, the use of a co-primary functional measure or proxy has been mandated for all CIAS studies. The exact type of functional co-primary or proxy measure is open to discussion with regulators.

In contrast, European regulatory bodies have taken a somewhat more lenient stance and have instead opined that a functional measure serving as a key secondary outcome would be enough to establish a treatment label[5]. However, European regulatory authorities typically require experimental deigns to be of longer duration than their US counterparts. Thus, designs establishing three or four months of efficacy data would not be considered to be of long enough duration and a minimum of six months of efficacy data would be needed for labelling purposes. In addition, a claim for a maintenance effect would need to be established for European regulators using a randomised withdrawal-type study design[5]. Once again, the exact programme characteristics may be open for discussion with regulators.

In summary, regulatory agencies are open to considering cognitive targets such as EF in ADHD, especially when there is preexisting data reflecting some consensus regarding the prominence, stability and time course of cognitive symptoms in a given indication. Recently, there has been a large increase in the number of studies assessing the effects of various pro-cognitive drugs on cognitive impairment associated with depression, ADHD, Parkinson's disease and bipolar disorder. Given issues regarding pseudo-specificity, it is important for drug developers to partner early with regulatory officials in order to design studies which will provide adequate data to overcome any issues regarding pseudo-specificity. There are several designs that have been sanctioned by regulatory authorities, that if implemented successfully would provide the type and amount of data needed to secure successful treatment labelling.

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