A drugs test

Aiswariya Chidambaram, Senior Research Analyst – Healthcare for Frost & Sullivan, considers the potential of the different neuropharmaceuticals on offer…

Neuropharmacology is defined as the branch of science that studies the effects of drugs on the cellular functioning of the nervous system. The two key disciplines of neuropharmacology are molecular neuropharmacology and behavioural neuropharmacology.

Both molecular neuropharmacology and behavioural neuropharmacology are closely interconnected, as they involve the interactions of neurochemical substances, such as neurotransmitters, neurohormones, neuropeptides, neuromodulators, ion channels, second messengers, co-transporters, enzymes and receptor proteins in the peripheral and central nervous systems (CNS). Neuropharmaceuticals or drugs used to treat CNS disorders target these neurochemical interactions in order to produce symptomatic or therapeutic effects.

Molecular neuropharmacology focuses on developing drugs that target neurochemical interactions between neurons and receptors on neurons, in order to treat neurological and mental disorders. The key neurotransmitters targeted by neuropharmaceuticals include GABA, dopamine, serotonin and acetylcholine, as they play a crucial role in controlling and coordinating body movements, mood and cognition. Behavioural neuropharmacology, meanwhile, deals with studying other effects of drugs on human behaviour, with a particular focus on drug dependence and substance addiction – for example alcohol, nicotine, caffeine and cocaine – and their effects on human brain.

Most neuropharmaceuticals exhibit their effects by targeting either the axonal or synaptic processes of neuron communication or by modifying the signal transduction process. Those that focus on axonal processes inhibit neuroexcitation by membrane stabilisation, chelate intrinsic ions or infuse extraneous ions. On the other hand, neuropharmaceuticals that target the synaptic process inhibit neurotransmitter synthesis, neurotransmitter reuptake, neurotransmitter binding to receptors and enzyme degradation; facilitate or inhibit neurotransmitter release; and produce compounds that mimic neurotransmitters but do not have post-synaptic efficacy.

In addition to this, the processes used to modify synaptic activity can also be employed to interfere with the signal transduction processes, particularly second messenger activity.

The key drug classes used to treat CNS disorders can be broadly classified into two types: drugs for neurological disorders – including anti-Alzheimer's drugs, anti-Parkinsonian drugs, antiepileptics and pain management drugs – and those used for mental disorders – such as antidepressants and antipsychotics, in addition to other drugs that are used to treat niche disorders, for example multiple sclerosis, attention deficit hyperactivity disorder, insomnia and restless legs syndrome.

However, given the increasing importance of neuropharmaceuticals that modify disease processes to enhance memory and cognitive functions, as in the case of Alzheimer's disease (AD), different hypotheses have been proposed by researchers for the classification of drugs based on their mechanism of action.

Beta-amyloid synthesis inhibitors

Beta-amyloid, produced by the proteolytic, sequential cleavage of the amyloid precursor protein (APP) by beta and gamma secretases, is the hallmark feature in the pathogenesis of AD. Consequently, amyloid synthesis inhibitors are primarily of two types, namely beta secretase/BACE inhibitors and gamma secretase inhibitors.

Beta secretase/BACE Inhibitors – only a small portion of the APP undergoes cleavage by the BACE inhibitors in an amyloidogenic pathway. Although it showed promising therapeutic effects in animal models, identification of small inhibitors for drug development poses challenges. A vast majority of the compounds are in the pre-clinical phases, with very few in Phase I stage.

Gamma secretase inhibitors – gamma secretase is a high molecular weight complex protein, acting on the cleavage products of alpha and beta secretases, leading to the production of beta-amyloid. Gamma secretases act on multiple substrates, particularly N-cadherin and notch, and the inhibition of this enzyme could induce toxicities, owing to their direct impact on the notch signalling pathway. Hence, the focus of development revolved around second-generation gamma secretase inhibitors that do not influence notch signalling pathways.

Amyloid plaque inhibitors

This mechanism focuses on two important aspects of AD, which include beta-amyloid plaques; a reservoir of beta-amyloid that can diffuse and cause tau phosphorylation over the course of several years; and aggregated A-beta 42, a potent stimulator of microglia and the subsequent

Neurological disorders		
Drugs	Classification by mechanism of action	Leading brands
Anti-Alzheimer's drugs	Acetylcholinesterase inhibitors	Aricept, Reminyl/Razadyne, Exelon
	N-methyl, D-aspartate receptor antagonists	Namenda, Ebixa, Axura
Anti-Parkinsonian drugs	Dopaminergics	Madopar, Sinemet
	Dopamine agonists	Mirapex, Cabser/Dostinex, Requip
	Catechol-o-methyltransferase inhibitors	Comtan, Stalevo
Antiepileptics	Traditional anti-convulsants	Depakote/Valcote, Depakine,Tegretol
	Second Generation anticonvulsants	Neurontin, Topamax, Lamictal
Pain Management Drugs	Non-steroidal anti-inflammatory drugs	Tylenol, Aspirin, Ultracet
	Opioids	Duragesic, Oxycontin, Sevorane/Ultane
Mental disorders		
Antidepressants	Selective serotonin reuptake inhibitors	Zoloft, Paxil, Lexapro
	Selective norepinephrine reuptake inhibitors	Effexor, Remeron, Cymbalta
Antipsychotics	Typical antipsychotics	Thorazine/ Largactil, Loxapac, Haldol, Phenotil
	Atypical antipsychotics	Seroquel, Zyprexa, Risperdal, Abilify

Classification of drugs used to treat CNS disorders

chronic inflammatory reactions. Most of the amyloid plaque inhibitors are based on antibody technology. It is important to facilitate beta-amyloid clearance due to the neurotoxicity of soluble A-beta 42.

Tau aggregation inhibitors

Tau is an axonal protein that promotes the assembly and stability of microtubules in healthy neurons and its phosphorylation is regulated by kinases, such as GSK-3 beta and CDK-5, as well as phosphatases. The hyper-phosphorylation of tau, thought to be induced by soluble amyloid-beta 42, leads to neurodegeneration by microtubule disruption, and the resulting neurofibrillary tangles block neurotransmission and axoplasmic transport.

Nicotinic acetylcholine receptor agonists

One of the key areas of focus in AD is the deficiency in cholinergic neurotransmission owing to the selective loss of cholinergic neurons and nicotinic acetylcholine receptors in the hippocampus, which influences the cognitive performance of an individual and offer neuroprotection against beta-amyloid-induced cytotoxicity. Stimulation of these receptors is considered to improve cognitive impairment in AD patients and counter the losses of synapses and neurons.

Muscarinic receptor modulators

The majority of the amyloid precursor protein (APP) is processed by the alpha-secretase enzyme in a non-amyloidogenic pathway. Muscarinic receptor agonists are considered to trigger this non-amyloidogenic cleavage of APP, resulting in reduction of beta-amyloid levels. Thus, muscarinic receptor agonists find potential application not only in the symptomatic treatment of AD, but also influence the progression of the disease.

5-HT (serotonin) receptor modulators

It is hypothesised that the loss of serotonergic neurons not only leads to cognitive decline, but also behavioural symptoms such as anxiety, depression and insomnia. However, there are seven major classes of 5HT (serotonin) receptors, and it is not yet clear as to which receptor subtype needs to be inhibited or stimulated to improve cognitive or behavioural symptoms in AD patients. The 5-HT(4) and 5-HT(6) subclasses are being extensively studied, as agonists of these receptors are considered to enhance memory performance, cognition and behavioural symptoms in AD patients.

Ion channel modulators

It has been hypothesised that the dysregulation of calcium homeostasis is likely to play a crucial role in accelerating some of the pathological processes in AD. Interestingly, the underlying biochemical events – such as activation of calcium channels, disruption of intracellular calcium stores and subsequent production of free ions by calcium-sensitive enzymes – lead to neuronal death in AD patients.

The critical function of calcium signalling is backed by two facts. Firstly, mutated presenilins in patients with familial history of AD facilitates beta-amyloid generation due to the elevated cytosolic calcium concentration. Secondly, the molecular mechanism of the already approved memantine conforms to the prevention of excessive calcium influx via the NMDA receptor-mediated ion channel, thereby protecting cells from glutamate toxicity and cell death.

Chelating agents

It is believed that amyloid-beta aggregation is partially dependent on metal ions, such as copper (Cu) and zinc (Zn). This is based on the fact that A-beta 42 can be precipitated by Zn and radicalised by Cu, and that both metals are significantly accumulated in plaques. Therefore,

Cu/Zn chelating compounds are anticipated to induce A-beta 42 solubility and prevent plaque formation.

Phosphodiesterase (PDE4) inhibitors

Phosphodiesterase inhibitors help in prolonging cAMP signalling, which plays a key role in processes regulating memory and cognition performance by counteracting deficits in long-term memory, as a result of over-expression of mutant forms of APP. Additionally, PDE4 inhibitors are also known to offer neuro-protective, neuro-regenerative and anti-inflammatory effects.

Vaccines

Vaccines involve the active or passive immunisation of AD patients with fibrillar amyloid-beta, resulting in the production of anti-amyloid antibodies. This mechanism has been explained by two hypotheses. Firstly, antibodies are considered to bind amyloid plaques and trigger amyloid beta aggregation by microglia. Secondly, circulating antibodies may bind soluble amyloid-beta in the periphery, thereby causing an amyloid-beta efflux from the brain, commonly referred as the peripheral sink hypothesis.

The other less researched drug classes include those such as AMPA receptor agonists, H3 receptor antagonists and neuroprotective compounds. It is important to note that none of the AD-modifying drugs have reached the market to date, although a few of the compounds have reached Phase III level of clinical development, which include Bapineuzumab from Pfizer and Janssen and Solanezumab from Eli Lilly.

Neurological disorders – key focus areas for R&D

Research and development of drugs for CNS disorders is a complex, risky, capital-intensive and lengthy procedure, as compared to other therapeutic areas, owing to the high chances of failure associated through the various phases of clinical development. It is estimated that approximately 92% of anti-AD compounds fail during clinical experimentation stages and 98% of CNS drug candidates don't cross the blood-brain barrier. Thus, such complexities pose a major threat to new market entrants, particularly for medium and small-sized pharmaceutical/biotechnology companies.

In addition to this, the patient recruitment process and duration of clinical trials remain a challenge to drug developers. Although several specific initiatives have been undertaken by European governments to raise funding for research projects and awareness campaigns, the overall finance from the public sector is still at much lower levels as compared to other major diseases.

Neurodegenerative diseases

Alzheimer's disease

AD, the most common form of dementia, is a progressive, chronic, neurological disorder with symptoms such as memory loss, personality alterations, and difficulty communicating and performing routine tasks. The beta amyloid plaques formed on the surface of brain cells and the neurofibrillary tangles (tau protein) formed inside the cells are considered to be the two most important hallmark features of AD.

Although research has gone a long way in establishing an understanding of the underlying mechanism and etiology of AD since its discovery in 1906, scientists have not yet reached a consensus and have hypothesised a large number of disease mechanisms. This clearly reflects the lack of an effective therapy option or cure for the disease to date.

Parkinson's disease

Parkinson's disease, the second most common progressive, chronic neurological disorder is characterised by motor symptoms such as paralysis or tremors in the legs, hands, face, postural instability and bradykinesia – slowness of movement – as well as behavioural issues. The exact cause of the disease is unknown, although some of the symptoms are thought to exist due to the death of brain cells in the substantia nigra region, which is responsible for producing the dopamine that facilitates the smooth coordination of bodily movements.

Diagnostic techniques

Diagnosis of certain neurological disorders, such as AD in its initial stages, still remains a challenge, as minor memory problems are mistaken for general signs and symptoms of old age, and there is no single test that can diagnose the disease with 100% certainty. Several advanced diagnostic techniques – such as the cerebrospinal fluid analysis of phosphorylated tau protein and A-beta 42 peptide – and functional neuroimaging techniques – including Single Photon Emission Computed Tomography imaging, fluorodeoxyglucose imaging and amyloid Positron Emission Tomography scanning – are being extensively researched in laboratories for the early and accurate diagnosis of AD at its various stages of progression.

Disease-modifying drugs

As the existing drug classes for certain neurological disorders, such as AD, offer poor therapeutic efficacy and are only capable of providing symptomatic relief to patients, the core focus of R&D revolves around novel, disease modifying drugs, as they are safer, more efficacious, and aim to prevent or slow down progression rather than simply improve disease symptoms. As a result of this, the disease modifying drug class is likely to command premium pricing and drive the growth of the AD medication market in a significant way.

Genetics

Familial history and genetics are considered to be important risk factors for neurodegenerative diseases. Abnormalities in four genes on chromosomes 1, 14, 19 and 21 are thought to be strongly associated with an increased risk of developing AD. Apolipoprotein E4 (APO-E4) is identified as the strongest risk gene so far. Similarly, Parkinson's disease is suspected to be associated with certain hereditary links and the genes involved in this have been implicated. However, it has been discovered that hereditary factors have a less profound effect when compared to environmental factors, such as pesticides.

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