The great neuro-pipeline 'brain drain' (and why Big Pharma hasn't given up on CNS disorders)

Central Nervous System (CNS) disorders bear an economic burden of more than $2 trillion in the US and EU and rake in upwards of $80 billion a year for the pharmaceutical industry. Yet they have become as much a vice as a potential virtue. A novel Alzheimer's disease (AD) medication bears every promise of outshining the likes of Lipitor in blockbuster status, but its chances of reaching the market are also nearly 50% lower, and development costs 30% higher, than those of its cardiovascular counterpart.

By Julia Skripka-Serry

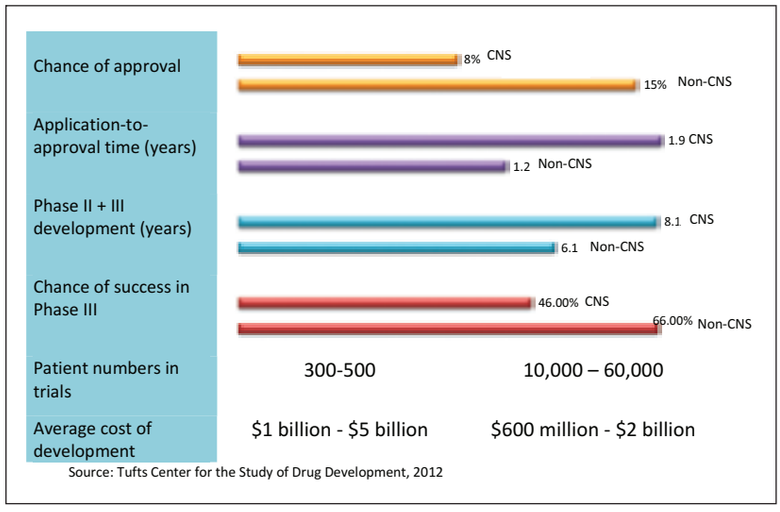
The high risk and low approval rates of drugs targeting diseases such as Alzheimer's, Parkinson's, depression, anxiety, schizophrenia and stroke have sent billions of dollars down the drain in recent years. While 85% of investigational compounds never see the pharmacy shelf anyway, the sheer financial scope of failures of neuro-leads in late-stage pipelines has made CNS drug development a literal brain drain.

No wonder Big Pharma seems to be turning its back on CNS drugs. Since 2011, GSK, AstraZeneca and Novartis have announced closures of neuroscience divisions globally. Meanwhile Pfizer, Sanofi, Janssen and Merck have begun to significantly downsize CNS operations. Few remain in the race. And who can blame them, when CNS drug development can cost billions more than any other therapeutic area, yet has a 45% higher chance of failure than drugs targeting other disorders (**Table 1**).

In 2012 we witnessed a fascinating race to the finish line between two anti-β amyloid monoclonal antibodies – Pfizer/Johnson & Johnson's Bapineuzumab ('Bapi') versus Eli Lilly's Solanezumab ('Sola'). Both contenders tried to make history by altering the Alzheimer's disease treatment paradigm, but ended up failing in two of the biggest Phase III studies of the year, having each likely spent upward of $600 million to develop the drugs[1].

Lilly and Pfizer were not the only drug developers to be plagued by CNS pipeline disasters. Baxter's Alzheimer's lead Gammagard failed to slow disease progression in Phase III Alzheimer's trials in July 2013, while a promising smaller biotech Satori Pharma has had to completely shut down operations after a disastrous trial performance of its lead AD compound SPI-1865 in May 2013.

Still in the AD race are Merck with MK-8931, an investigational inhibitor of beta secretase-1 (BASE), an amyloid precursor, and Roche with gantenerumab, an anti-A antibody treatment which has so far failed to impress analysts and clinicians. Despite strangling



Source: Tufts Center for the Study of Drug Development, 2012

Table 1

its own CNS R&D efforts back in 2011, Novartis has emphasised that it will merely be adopting a novel strategy on neuropharmaceutical development, focusing instead on genetics of brain disorders.

It is this 'restrategising' which is likely to become representative of the Big Pharma industry. Rather than pronouncing the death of CNS R&D, we may expect to see shifts towards risk-lowering activities such as cost-diluting partnerships, increased in-licensing and M&A activity, and a heavier focus on preventing failures at earlier stages of development through improved *in silico* modelling.

Reasons for major CNS drug failures

For the most part, the extortionate CNS R&D losses of recent years are due to the fact that the majority (4 out of 5) of neuropsychiatric leads fail in the pricey Phase III stage of clinical trials. Reasons for the neuro-failures are numerous, ranging from stricter FDA regulations for CNS disorders to insufficient understanding of mechanisms underlying brain disease. Lilly's Solanezumab, for instance, failed because the drug did not reach its cognitive and functional endpoints in a placebo-controlled study, outperforming placebo by a mere 1.41 points on the standard ADAS-cog Alzheimer's disease and dementia trial assessment scale.

To begin with, clinical trials involving disorders of the brain are notoriously difficult to set up and run. In addition to rather outdated (in the context of modern tools) assessment criteria and ambiguous endpoints, patient selection for diseases such as Alzheimer's, for instance, can take years to complete. The matter is further exacerbated by relatively poor diagnosis techniques. Other than performing cognitive ability tests and looking out for the presence of amyloid plaques and neurofibrillary tangles in the brain, we have little way of determining the true stage of AD advancement in patients. It is possible to have a cohort of patients in a clinical AD study among which disease progression would vary drastically, making it extremely difficult to observe a drug's effect on a group. And, while most investigational AD drugs have so far targeted the signature amyloid plaques, many studies now suggest that the plaque stage of Alzheimer's is a much-too-late phase at which to commence treatment. Many new AD medication studies are looking into prophylaxis for patients determined to be genetically at risk, rather than focusing on post-symptomatic treatment *per se*.

Another common hindrance in CNS trials is the Placebo Effect. Traditionally, the placebo effect was noted in clinical trials where control patient cohorts unknowingly taking sugar pills coerced themselves into recovery by believing they were being treated. An overwhelming number of clinical trials, in particular trials which are conducted with the use of questionnaires, have failed because placebo pills were shown to be more than, or at least as effective as, the drugs being tested. That is to say, the compounds in trials were able to improve the patients' conditions, only the placebo improved them even more. Opposite to the placebo effect is the 'nocebo' effect, whereby patients get worse because they realise they are being administered placebo. The only way to definitively discern between therapeutic recovery and the placebo effect is to devise better diagnostic tools which help visualise, assess and quantify the drugs' effects in the brain.

Despite the drawbacks, Big Pharma cannot afford to quit CNS

Neurological disorders significantly outnumber diseases in other therapeutic areas, inflict higher treatment and loss of productivity costs than cancer, cardiovascular disease and diabetes put together and are growing in incidence faster than any other disease class in the EU and the US. More than 600 known neurological disorders now top the leading disease list in the developed world (**Table 2**). In Europe, 38% of the population is said to be affected by brain disorders annually[2], whose burden in 2010 was estimated to be €798 billion. Over the coming years, the European Brain Council has forecasted a further 20% increase in neurologic illness in the EU[3].

To exacerbate the problem, ageing populations have never before borne so much impact on the global total. As cardiovascular, infectious and

Table 2: The cost and burden of leading neurological disorders in the United States 2010-11

Disease	Prevalence/ Incidence	Economic Burden (incl. prod. loss) (US$)	Available treatment(s)
Chronic pain	50 million	635 billion	OTC pain relievers, anti-inflammatory steroids, therapy (physical & psychological), Medical Devices: Neurostimulators, Patient Controlled Analgesia
Depression (major)	46.4 million	16 billion	Medication: Selective serotonin reuptake inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors (SNRIs), Norepinephrine and dopamine reuptake inhibitors (NDRIs), others; Medical devices: deep Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS)
Migraines/cluster headaches	37 million	20 billion	OTC pain relievers, anti-inflammatory steroids, tripans, ergotamines, triptan+anti-emetic combination therapy, Botulinum toxin (Botox)
Hearing loss/deafness	37 million	14.75 billion	Hearing aids, cochlear implants
Bipolar disorder	5.7 million	42 billion	Mood stabilizers: Lithium, anticonvulsants, antipsychotics; Antidepressants,; Medical device: deepTMS (under investigation by Brainsway Israel)
Alzheimer's disease	5.4 million	216 billion	Cholinesterase inhibitors: donepezine, rivastigmine, galantamine; Glutamate blocker: memantine
Autism spectrum disorders	3.5 million	35 billion	Virtually no medication – antidepressants occasionally used to treat symptoms; educational programs
Schizophrenia	3.4 million	32 billion	Typical antipsychotics, Atypical antipsychotics; Medical device: deepTMS (under investigation by Brainsway Israel)
Epilepsy	3 million	17.6 billion	Anti-epileptic drugs (AEDs): sodium valproate, carbamazepine, lamotrigine, topamax, vigabatrin; Medical device: VNS
Brain/head injury	1.7 million annually	48 billion	Neurosurgery, physical therapy
Blindness	1.3 million		Retinal prosthesis, visual cortex neuroprosthesis (under development), stem cell therapy (under development)
Stroke	795,000 annually	38.6 billion	Hemorrhagic: anticoagulants, surgery; Ischemic: clot busters, surgical clot removal (3-4-hour window); Sphenopalatine Ganglion (SPG) stimulation (24-hour window—under investigation by BrainsGate Israel)
Parkinson's disease	500,000	23 billion	Levodopa; Dopamine agonists: pramipexole, ropinirole; Catechol O-methyltransferase (COMT) inhibitors, Monoamine oxidase-B (MAO-B) inhibitors; Medical devices: Activa® implanted brain stimulator, deepTMS (under investigation by Brainsway Israel)
Multiple sclerosis	400,000	10 billion	Interferon-beta-1a and -1b, glatiramer acetate, mitoxantrone, natalizumab, fingolimod, teriflunomide, dimethyl fumarate; Stem Cell therapy: currently in clinical trials
Spinal cord injury	12,000 annually	14.5 billion	Neuroprosthetics, Stem Cell Therapy, antioxidant medication (methylprednisolone, lazaroids)
Amyotrophic Lateral Sclerosis (ALS)	5,600 annually	6 billion	Riluzole (only FDA-approved medication); Clinical trials: Arimoclomol, tirasemtiv, NurOwn™-adult stem cell therapy (under investigation by BrainStorm Cell Therapeutics Israel)

oncology treatments ameliorated, higher survivability meant that the incidence of diseases of 'old age', such as dementia and AD, strokes, Parkinson's disease and progressive hearing loss, increased. AD and stroke have been identified as the fastest-growing threats to US health, ahead of autoimmune disorders and diabetes[4].

Despite the high risks, the rewards of developing the next AD medication appear to be much higher. Indeed, even a relatively mediocre Alzheimer's treatment approved by the FDA could break a new blockbuster sales record. And this is why, despite varying strategies, almost all Big Pharma players are keeping one foot sturdily in the door when it comes to neuropharmaceutical development.

Reliable CNS targets are lacking

Virtually all CNS disorders beg for novel, more target-specific medications. Most neuropharmaceuticals on the market today have come about serendipitously, through observation that certain drugs improved certain symptoms, rather than through research tailored to the disease. In fact, an overwhelming majority of brain medications, the likes of which are Thorazine, Valium, Prozac and Xanax, have widely unknown mechanisms of action, despite having been discovered as early as the 1940s. And nearly all CNS treatments today treat symptoms, rather than modify the disease. The reason for this is that many CNS drugs target very general neurotransmitters in the brain, such as dopamine, serotonin, norepinephrine and acetylcholine – molecules involved in an infinite number of downstream signalling pathways. It is because of this generality that neuropharmaceuticals work 'somewhere down the line', at the same time carrying so many unwanted and dangerous side-effects, and exhibiting such sub-optimal efficacy (many leading anti-depressants faired only as well as, if not worse, than placebo in recent clinical trial re-runs).

Although new anxiolytics, antidepressants and anticonvulsants do emerge on the market frequently, they are merely 'me-too' drugs with tweaked chemistry, rather than innovative molecules targeting novel pathways. Unless novel CNS targets emerge, cheap 'me-too' generics will continue to flood the market, further disincentivising drug developers. In order to introduce truly innovative treatments on the neuro-market, basic neuroscience must catch up with the growing global demand for precise therapeutic targets.

Promising advancements are on the way

The complexity of grey matter easily makes it the most challenging therapeutic target. The colossal

scope of heavily interconnected brain microcosms, such as the intricate network of neuronal connections (the 'connectome'), the densely populated molecular environment, and the binary patterns of electrophysical behaviour of neurons, in addition to individual genomics and metabolomics, is proving to be no easy matter to ponder even for absolute experts in the field. Nonetheless, novel discoveries in genetics, molecular neuroscience and computer-aided lead generation, as well as altogether out-of-the-box neurotech disruptions to conventional drug discovery, have made shifts in new directions likely to be luring Big Pharma back towards brain R&D. Perhaps most encouragingly, the massive brain research initiatives, such as the B.R.A.I.N in the US, the Human Brain Project in the EU and Israel Brain Technologies in Israel, are all likely to begin feeding much-needed therapeutic targets to the pharmaceutical industry in the near future.

Electro-stimulation and electroceuticals

There is a strong relationship between the electrical and molecular layers of the brain. Molecular changes are likely to cause changes in the firing patterns of neurons. Meanwhile, physically exciting or suppressing the electrical activity of neurons results in changes to synaptic neurotransmission of various molecules. Electric brain stimulation is an up-and-coming practice which offers more precision and less side-effects in the treatment of disorders whose location in the brain we have been able to elucidate.

Deep Transcranial Magnetic Stimulation (deepTMS), for instance, is a novel, non-invasive FDA-approved therapy to-date found effective in the treatment of Parkinson's disease, depression, chronic pain and schizophrenia. DeepTMS involves magnetic activation of regions deep (up to 7cm) within the brain. The stimulation can be applied at virtually any 3D brain co-ordinates, thus the more we map the brain, the more useful the treatment becomes.

Meticulous brain mapping could also potentially culminate in the birth of a highly lucrative, albeit yet non-existent, treatment: electroceuticals. Despite the fact that they do not yet exist, electroceuticals have been all the rage lately, promising scrupulously tailored ways to modulate action potentials of neurons, treating anything from hypertension to headaches. Electroceuticals would exist in the form of nano-particles able to deliver action potentials to specific locations within the body. Technically, the electrode chips already in use in neural prosthetics, or research tools such as optogenetics, which allow light-triggered activation or inhibition of individual neurons, attest to the realistic possibility of electroceutical development.

Novel, precision CNS diagnosis tools

Perhaps the best salvation for Big Pharma's CNS efforts could come in the form of more concrete endpoints in clinical trials. According to Thomas Insel, the director of the National Institute of Mental Health (NIMH) in the US: "Unlike our definitions of ischaemic heart disease, lymphoma or AIDS, the DSM (Diagnostic and Statistical Manual of Mental Disorders) diagnoses are based on a consensus about clusters of clinical symptoms, not any objective laboratory measure. In the rest of medicine, this would be equivalent to creating diagnostic systems based on the nature of chest pain or the quality of fever." Indeed, despite the sophistication of the pharmaceutical industry today, CNS clinical trial assessment still relies on symptom manuals, some of which were written nearly half a century ago. But the pressing need for more accurate tools means steps in the right direction are being made.

Biomarkers, for instance, are molecules which signal the presence of disease. In diagnostics, biomarkers are molecules introduced into the body, which can be modified by the body in such a specific way that their modified form can give an indication of the presence, stage and progression of disease. Additionally, genetic biomarkers are genes or gene segments which can signal a certain individual's probability of response to a particular medication. Unsurprisingly, the CNS biomarker market niche is growing faster than any other biomarker sector. In the future, bio- and genetic markers are likely to form the basis of personalised neuro-medicine.

Another promising neurodiagnostic tool is currently being developed by the medical device start-up ElMindA. Brain Network Activation (BNA) is a non-invasive brain scanner technology which combines EEG readings with powerful analytical algorithms in order to record 'signature' patterns of neural activity within the brain. The technology can be used to compare neural network maps before and after drug administration, or during post-injury recovery. On several occasions ElMindA has now been able to demonstrate that administration of certain drugs yields distinctly altered activity networks.

Finally, as academic labs plough on with CNS gene sequencing, genetic profiling will inevitably be at the centre of CNS clinical trials in the future. For instance, if a vast enough combination of genes related to Alzheimer's disease becomes known,

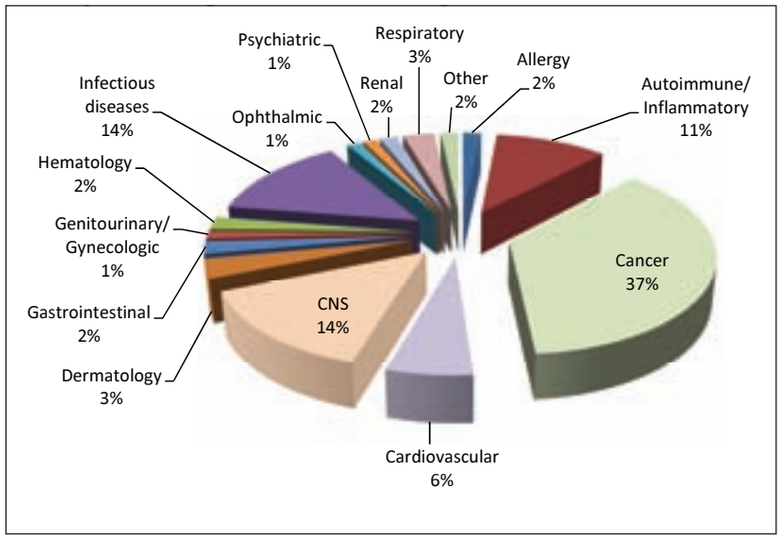


Figure 1
Therapeutic area segmentation of 220 licensing deals in 2012

patients who are at high risk of developing the disease can be selected for clinical trials years before they develop any symptoms.

Neurogenesis and stem cell transplants

Just six years ago aspiring neuroscientists would have been taught that brains are born with a set amount of neurons, and, while new synapses are able to form throughout a lifetime, new nerve cells are no longer generated within the brain. But researchers have recently documented neurogenesis in several brain areas: the hippocampus, the olfactory bulb and the subventricular zone. Brain therapies involving stem cells thus have the potential to revolutionise CNS treatments in the future.

Trends and directions in CNS drug development

Generally, traditional in-house CNS R&D is waning in the Big Pharma world. But perhaps rather erroneously this is interpreted as a sign of abandonment, rather than a sign of new business strategies being developed. The fact of the matter is, the glory days of the R&D department were numbered long ago. Today, spending cuts, lack of molecular understanding of brain disease and a pressing need to dilute risk mean that the same processes cannot continue to run in the industry under a completely different set of parameters. R&D departments are being swapped for risk-sharing partnerships with other Pharma or smaller biotechs and 'traditional' research models are abandoned in favour of more innovative, and much less cash-intensive, activities. Mitigating risk is at the core of the less bulky Big Pharma 2.0.

Partnerships and in-licensing on the rise

Nowadays, the vast majority of neuropharmaceutical development is being conducted on a partnership or collaboration basis. Most commonly, a smaller biotech's trials will receive 50-100% of funding from one or more Big Pharma players, on conditions of key milestones being met. In the case of poor trial results, the Big Pharma partner may withdraw from the deal at any time. Because larger players tend to embark on such partnerships at later pipeline stages, they significantly cut the costs of earlier development and avoid all the risks associated with it.

In 2012, CNS was responsible for 14% of all pharma licensing deals – second only to cancer (**Figure 1**). The trend continued steadily in the first half of 2013, with 15% of all licences being CNS[5].

Risk modelling and statistical predictions

At a time when millions of dollars can no longer be thrown at well plates in hope that something will stick, mathematical risk modelling can come to play as crucial a role in the pharmaceutical industry as it does in economics. Expected Net Present Value (eNPV) was a widely used economic valuation formula recently used to demonstrate the value of cutting risk in a CNS clinical trial. Calculations using eNPV demonstrated that cutting risk in an average CNS trial by just 1% could save more than $5 million[6]. Statistical research such as this is expected to be on the rise, as more mathematical power is dedicated to controlling costs and risk for the pharmaceutical industry.

Continuing need for government and academic co-operation

With Big Pharma tending to later-stage M&A and in-licensing, someone must be picking up the bill of preclinical and early-stage research. In 2012, cancer topped the list of government R&D spending in the US, followed closely by dementia. Yet dementia burden is 12 times that of cancer and its incidence outpaces all other disorders. Clearly, more needs to be done for CNS disorders on the basic level, but if Big Pharma players want to reap the rewards offered by CNS research, they should expect to contribute, too.

And many do. The Israeli generic giant Teva, whose strategy in recent years made a pronounced shift towards innovative R&D, invested $15 million into 50+ CNS research projects at universities across Israel. In addition to helping out with basic research, the company hopes to get first dibs on important therapeutic targets, getting a substantial head-start on drug development.

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More hope for genetics of brain disease

Merck, Roche, GSK and AstraZeneca have recently established dedicated CNS genetic research and sequencing units in order to bolster their personalised medicine capability and to identify genetic biomarkers which can be used in clinical trials. Genes signalling disease can take nearly all the guesswork out of pre-selection patient diagnosis in clinical trials. Once important gene markers are identified, patient selection is likely to become much more accurate, simple and reliable and will likely significantly improve trial outcome, perhaps even with previously failed drugs.

***In silico* R&D**

With increasing computer power and growing protein structure databases, molecular computer modelling may soon become a great tool for cutting costs in clinical trials. AstraZeneca recently launched a virtual Neuroscience Innovative Medicines Unit (iMed) with about 40 'neuro-IT' employees. The goal of iMed will be to create a vastly intricate computer network which would model anything from molecular interactions to whole clinical trials. According to AstraZeneca's vice-president of R&D information John Reynders: "The analogy would be … a 747 that you're flying, and yeah, you've got three or four guys flying this thing, but they also have a ton of computers up there." Whatever the premise, modelling is one of the most crucial tools which can and must be used by Big Pharma in order to avoid unnecessary expenditure on a bleak reality. DDW

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