Why is the global CNS pharmaceutical market so under-penetrated?

'The global CNS drug market must grow by >500% just to be comparable to the global market for cardiovascular drugs.'

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In 1998, the global market for drugs for central nervous system (CNS) diseases was US$33 billion, and this market constituted only 12% of the overall global pharmaceutical market, which was US$280 billion (http://www.reuters-businessinsight.com/). However, the global market for CNS drugs is actually smaller because a single class of drugs, selective serotonin reuptake inhibitors (SSRIs), comprises a large proportion of the global CNS drug market. Approximately 30% of all neuropharmaceuticals sold are for the treatment of depression and 70% of the antidepressants are SSRIs. Therefore, a single class of drug, the SSRI, forms 20% of the global CNS drug market. The non-SSRI CNS drug market is US$20 billion, which is less than a third of the global drug market for cardiovascular diseases, which was US$64 billion in 1998.

The number of individuals in the USA alone with cardiovascular disease (CVD) is ~40 million (http://www.americanheart.org/statistics/). This includes ~26 million people treated for hypertension and ~12 million with coronary heart disease. By contrast, the number of individuals in the USA that are afflicted with some disorder of the CNS is 80 million [1]. The ratio of annual revenues for heart and non-SSRI brain drugs, relative to the number of individuals afflicted with heart and brain disorders in the USA, is US$480 and US$75 per person, respectively (Figure 1). Therefore, the CNS drug market would have to grow by >500% just to equalize the CVD market. The actual discrepancy between the CVD and CNS markets is even larger, because 65% of the CVD market are people with hypertension, which is more of a risk factor for other diseases, including CNS disorders.

Undertreatment of most CNS disorders

The above analysis indicates that the global CNS drug market is under-penetrated by nearly a log order of magnitude. Indeed, certain brain disorders, such as depression, epilepsy, schizophrenia and pain have, in general, responded to conventional small-molecule neuropharmaceuticals. However, there are many neurological disorders that have so far been largely refractory to pharmacotherapy. These include:

- Alzheimer's disease;
- Huntington's disease;
- Stroke/neuroprotection;
- Brain cancer;
- HIV infection of the brain;
- The ataxias;
- Brain and spinal cord injury;
- Amyotrophic lateral sclerosis (ALS);
- Children with inborn genetic errors affecting the brain.

Patients with Parkinson's disease experience benefit from L-dihydroxyphenylalanine (L-DOPA) therapy, but there is no neuroprotective agent that prevents the progressive decline in function caused by this disease. Patients with multiple sclerosis have benefited by the suppression of the immune system in the periphery with cytokine therapeutics, but no drugs exist to abate the progressive demyelination and loss of function caused by multiple sclerosis.

Causes of CNS undertreatment

Why is the present-day pharmaceutical model not working for the majority of CNS disorders, and why is the global CNS drug market so under-penetrated? One explanation could be that the above diseases are serious disorders that are not really amenable to pharmaceuticals. However, there is an alternative explanation. Neuropharmaceuticals made today are lipid-soluble, small molecules. The drugs have to fit this model because only lipid-soluble small molecules cross the blood–brain barrier (BBB). To be more precise, only lipid-soluble small molecules with a molecular weight of <500 Da cross the BBB, and can enter CNS drug

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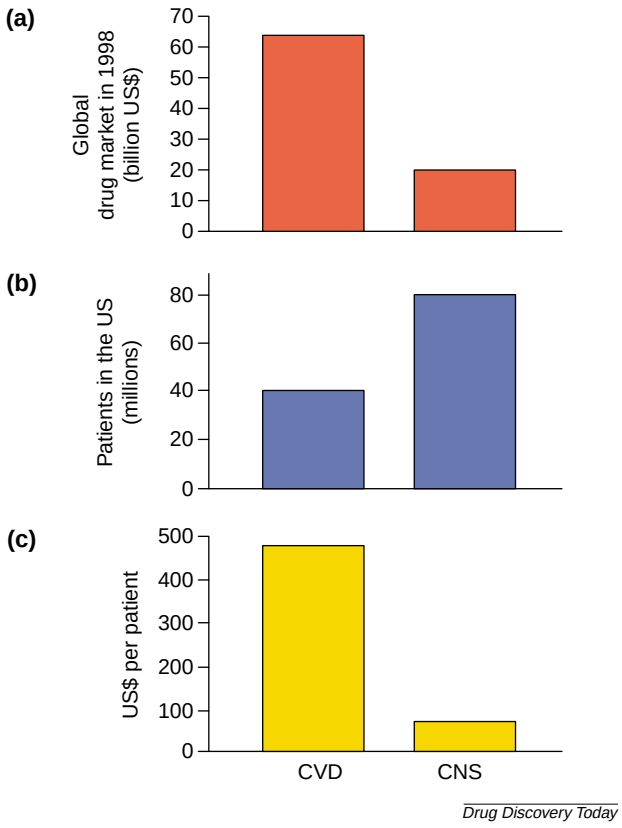

Figure 1. The global market in 1998 for non-SSRI drugs for the central nervous system (CNS) and drugs for cardiovascular diseases (CVD) **(a)** is plotted in parallel with the number of individuals in the USA with CNS or CVD disorders **(b)**. These data are used to compute the ratio of annual dollars spent per individual **(c)**, which shows a 6-fold higher ratio for CVD diseases relative to CNS disorders. This ratio was computed for the US market, which forms ~30% of the global drug market. The ratio is an approximation, and is intended to reflect the great disparity between the current size of the global drug markets for CVD and CNS disorders.

development [1]. The majority of small-molecule drug candidates do not cross the BBB because the drugs are water-soluble and/or have a molecular weight of >500 Da. In addition to small molecules, the large-molecule drugs (e.g. recombinant proteins, monoclonal antibodies, gene medicines, antisense drugs) are potential neuropharmaceuticals, but essentially all large-molecule drugs do not cross the BBB. Thus, water-soluble small-molecule drugs with molecular weights of >500 Da, or the large-molecule drugs, cannot enter CNS drug development because the drugs do not cross the BBB and because no brain drug (or gene) targeting technology is available. Therefore, by necessity, the only drugs that can enter CNS drug development are the conventional lipid-soluble small molecules, and these types of drugs do not treat the intractable neurological diseases listed previously. There are two models to explain the under-penetration of the global CNS drug market:

(1) The problem of poor drug transport across the BBB is a secondary issue, because the majority of the serious CNS disorders are refractory to pharmacotherapy *per se*; the diseases are simply resistant to drug therapy.
(2) The problem of poor drug transport across the BBB is the primary issue. The majority of CNS disorders are refractory to drug therapy, because >98% of all potential CNS drugs do not cross the BBB. The BBB problem reduces the number of potential drugs that can enter drug development to <2% of all potential drug candidates. It is possible that new drugs for the intractable brain disorders are found in the large pool of drugs that do not cross the BBB.

The BBB problem

Should the debate be resolved in favor of the view that the BBB is a primary problem in CNS drug development, then the pharmaceutical industry would find it difficult to establish internal BBB drug-targeting programs. This is because the BBB problem has been neglected for so long that there is very little worldwide BBB infrastructure (i.e. a pool of scientists trained in BBB that understands this area of science). Industry typically looks to academia to provide infrastructure for key areas of science, but the long-term neglect of the BBB field by academic neuroscience is entrenched. Therefore, the BBB problem is a situation where industry must provide the leadership and build the infrastructure for future progress in this crucial field. There are many initiatives that industry could take to improve the BBB infrastructure:

- Identify scientists in the company who are familiar with biological transport problems and form an initial BBB development group.
- Fund training programs in academia to encourage young scientists in either the neurosciences or the pharmaceutical sciences to develop careers in BBB research.
- Establish funding programs for research targeted to the BBB that emphasizes the molecular biology of brain endothelium and novel brain drug- or gene-targeting technologies. Much of the new research in the BBB field over the last 10 years has been devoted to '*in vitro* BBB' models using cell culture techniques, and these models provide a remote replication of the BBB properties that exist *in vivo*; thus, *in vivo* models should be encouraged.
- Consider the formation of industry cooperatives directed at the BBB problem, much like the single nucleotide polymorphism (SNP) consortium (http://snp.cshl.org/).

The reason that the global CNS drug market is so underpenetrated is that >98% of all potential drugs for the brain do not cross the BBB, and do not enter into CNS drug development. If the BBB problem were solved, then the number of small- or large-molecule pharmaceuticals that could enter CNS drug development would increase by 1–2 log orders of magnitude. In this event, the chance of finding novel therapeutics that treat the intractable CNS disorders would also be increased.

Reduction in healthcare costs

The size of the untreated CNS markets is so large that the future growth of the global neuropharmaceutical market could outpace the growth in the other sectors of the pharmaceutical industry. Better drugs for the brain would result in large savings in healthcare costs. Prolonging the age of onset of Alzheimer's disease by just five years could save an estimated US$50 billion per year in US healthcare costs (http://agingresearch.org/Advocacy/test1.htm). The development of a neuroprotective agent for stroke could reduce the healthcare costs for stroke rehabilitation, which is US$40 billion per year in the USA. Therefore, the increased portion of the healthcare budget devoted to an expanding neuropharmaceutical market would be more than offset by savings in healthcare costs that are no longer required for the chronic care of CNS patients.

Reference

1 Pardridge, W.M. (2001) *Brain Drug Targeting. The Future of Brain Drug Development*. Cambridge University Press

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