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Psychiatric Drug Development – A Dry Pipeline?



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Key Points

- Psychiatric drugs are among the most profitable products for the pharmaceutical industry.
- Despite this, investment in psychiatric drug development continues to decline.
- A major reason may be the fact that there has been no major breakthrough in this area of drug development for the last thirty years.
- Several “me-too” products have been launched, but the primary molecular action of psychiatric drugs remains the same since the first discovery of imipramine in the 1950s.

Nearly one in five Americans takes at least one psychiatric drug (Medco 2011). Twenty-five percent of Americans suffer from a diagnosable mental illness in a given year (Kaplan 2013). Mental disorders continue to plague people around the globe, and mental illness is a leading cause of impairment and disability across the globe (Greenberg 2013).

However, innovative medications for the treatment of depression, bipolar disorders, schizophrenia and other psychotic disorders are in serious decline. Over the last few years, the pharmaceutical industry has reduced its investment in psychiatric drug development. Big names like GlaxoSmithKline have actually closed down their entire psychiatric laboratories. Others, such as Pfizer and AstraZeneca, have reduced the size of their research programme and/ have closed down their internal research altogether (Hyman 2013).

While the Obama Administration has announced its BRAIN initiative, and the National Institute of Medical Health (NIMH) also promised to renew its efforts to stimulate research on the neurocircuitry of mental disorder, there is nothing significant to report on this front, and the psychiatric drug development pipeline remains relatively dry (Greenberg 2013).

Why is the Industry Retreating?

The question that arises is this: why are pharmaceutical companies retreating from this particular segment despite the fact that there is clearly an unmet need and there are numerous individuals out there who are struggling with mental disorders, and who remain symptomatic due to ineffective therapeutic options? Despite the fact that this product category is among the most profitable, why are industry leaders closing down their investment and instead diverting their funds into cancer, metabolism, autoimmunity and other disease areas? (Hyman 2013).

The most glaring reason for this retreat is that companies believe that therapeutic development in psychiatry is risky, time-consuming and difficult. They fear that the underlying science for psychiatric drug development remains immature and the path to understanding the very nature of mental disorders is too daunting. That is because most psychiatric disorders are too complicated to understand; their molecular and cellular underpinnings remain unknown and psychiatric diagnoses still remains arbitrary (Hyman 2013).

For companies operating with the goal of earning profits, discovering and developing novel and effective treatments for mental disorders just does not seem the right strategy. The process of drug development is not only time intensive, but it also costs a significant amount of money. It is estimated that the cost to develop a drug (including the cost of any failures) is approximately \$1.5 to \$2 billion. In addition, according to estimates by the Pharmaceutical Research and Manufacturers of America, it takes an average of ten to fifteen years for a new drug to actually complete the cycle from initial discovery to being available in the market (Kaplan 2013).

No Major Breakthroughs

If one examines drug development in psychiatry, it is evident that most drug development efforts have relied on the recycling of old drugs. Since

the 1950s, the primary molecular action of all antidepressants, anti-anxiety drugs and antipsychotic drugs remains the same. The first antidepressant, imipramine, which was discovered in 1957, altered the serotonin or norepinephrine levels in the brain. The antidepressants that are available today have the same mode of action. Antipsychotic drugs, both old and current, block dopamine D2 receptors (Hyman 2013). The entire psychiatric drug category comprises of “me too” drugs. There are six SSRI antidepressants and ten atypical antipsychotic drugs that perform the same function (Friedman 2013).

In addition, the efficacy level of these drugs has not changed significantly for many years. Whether you use imipramine or a more recent antidepressant, there is no dramatic change in efficacy. Apart from clozapine, all antipsychotic drugs have the same efficacy as chlorpromazine (Hyman 2013). While the drugs may have improved in terms of their safety and tolerability, as far as efficacy is concerned, it seems that goal has somehow become unachievable.

According to Robert H. Lenox, MD, Professor of Pharmacology and Clinical Neuroscience at the University of New England College Of Osteopathic Medicine, the frequency of drug failures in the central nervous system segment is particularly high. Drug candidates entering into Phase III can fail at a rate of 40 to 50 percent. In most cases, the cause of failure is lack of efficacy (Kaplan 2013).

Reasons For the Chronic Shortfall

So where are the breakthrough drugs? Where is that novel treatment that everyone is waiting for? What is the reason for this chronic shortfall in psychiatric drug development?

There are many factors at play here. The central nervous system is excessively complex. The preclinical models of psychiatric disorders are unsatisfactory. Diagnosis of psychiatric disorders is mainly based on subjective assessments. Disorders like depression have complex aetiology, and large-scale clinical trials of psychiatric drugs have not shown any promising results. How is the industry expected to invest its resources in a segment with so many complications? If one evaluates the point of view of the drug companies, one would realise that they are not entirely to blame. They have spent decades in research and have invested billions of dollars, but have yet to discover a single novel drug within the last thirty years (Fibiger 2012).

Possible Solutions

What the pharmaceutical industry needs is a new paradigm. As Lenox points out, “there is a dearth of valid new targets and novel drug candidates. Pharmaceutical companies often compete on the same poorly validated targets, wasting time and resources in the absence of early stage sharing of lead compounds and data . . . this is unsustainable as a business model” (Kaplan 2013).

What the industry needs to do is to rethink the process of drug discovery in this particular segment. They need to review the type of preclinical models and the classification and selection of patients in clinical trials. They need to make efforts to integrate advances in molecular, cellular and systems level knowledge of psychiatric disorders. Only then could there be any hope for the revitalisation of drug discovery in psychiatry (Psychiatric drug discovery on the couch 2007).

The above discussion in no way gives pharmaceutical companies a free pass as far as the process of drug discovery in psychiatry is concerned. In fact, some believe that it is the big companies who are primarily responsible for this crisis. According to Richard Friedman, MD, a Cornell psychiatrist, “The pharmaceutical industry is making a mistake, by running away from the brain just when things are getting interesting” (Friedman 2013).

However, it is not smart to place the entire weight of drug discovery on pharmaceutical companies. This is mainly because they are driven by profit motives. They are afraid to take financial risks, especially in a category that is significantly complex. However, academic researchers do not have the same fears. They are free to experiment and to take risks. That is why programmes like the Brain Activity Map (Alivisatos et al. 2012) and gene-sequencing technology can help identify genes and circuits that could be linked to mental disorders. If such connections are made, it would be easier to identify new targets for drugs, and would eventually motivate pharmaceutical companies to reinvest in drug development in psychiatry (Friedman 2013).

If innovation is to be achieved, then changes in psychiatry also need to take place, in both the preclinical and clinical domains. Rational drug design for psychiatric diseases can only be achieved if there is more investment in neuroscience. Academic researchers and scientists need to become involved.

Conclusion

Knowledge is the basic ingredient for any drug development process. A perfect example is cancer. Drug development and advancement in cancer was driven by a greater biological understanding of the disease. The same is true for psychiatric disorders. More information is needed about delusions, hallucinations and negative symptoms and more emphasis should be placed on fundamental research.

There needs to be a greater understanding of the psychological, cognitive and behavioural aspects of specific disorders. Knowledge about specific brain circuits and their role should be increased and this knowledge should then be linked to clinical phenomena. What is needed is an acceptance of the fact that the medical world is still quite ignorant about the disorders of the central nervous system. Once this fact is acknowledged, measures can be taken to overcome this ignorance and invest in neuroscience research, which will essentially lead to drug development and therapeutic advancement (Fibiger 2012).

All is not lost, however. A latest report by the Analysis Group highlights that there are potential new medicines in the global pipeline and there are some psychiatry drugs in the preclinical stage. The search for a “blockbuster drug” is being replaced with finding “niche buster drugs” (Kaplan 2013). Hopefully, a change in approach and more specific targeting will start a new phase in psychiatric drug development.

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