EDITORIAL

Moving psychopharmacological drug development to the developing world

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For a medical discipline to progress, there should be advances not only in the understanding of disease, but also in the treatment thereof. There were spectacular breakthroughs in the treatment of psychiatric disorders in the middle decades of the 20th century; these were the introduction of electroconvulsive therapy, mood stabilizers, neuroleptics, monoamine oxidase inhibitors, tricyclic antidepressants and benzodiazepines.[1,2] With the exception of the rediscovery of clozapine,[3] subsequent advances heralded improvements in acceptability and tolerability but not necessarily overall efficacy.[4] Examples of such advances were the introduction of the selective serotonin reuptake inhibitors and other newer antidepressants, and the introduction of the atypical antipsychotics.

Whereas there has been good news on some fronts, such as the introduction of phosphodiesterase 5 inhibitors for erectile dysfunction and the introduction of cholinesterase inhibitors and memantine for dementia, the psychopharmacological management of major mental illness has hit a brick wall.[5,6] There have been unimpressive or disappointing results with innovative treatments such as S-adenosyl methionine, L-methylfolate, omega-3 fatty acids, glutamatergic agents, neuropeptides and many others. This has even resulted in opinion being expressed that the future of psychopharmacology in schizophrenia appears bleak[5] and that the pipeline for psychiatric drugs has run dry.[7]

Without a proper understanding of the pathophysiology underlying major mental illness, treatment breakthroughs must rely on serendipity. Subsequent drug development would likely target incremental advances, based on me-too approaches. However, me-too approaches cannot be indefinitely pursued and there is a limit to how commercially successful such me-too drugs will be. There is a long list of other reasons, as well, why research and development of neuropsychiatric drugs is difficult and economically challenging.[8] Many leading multinational pharmaceutical companies are therefore downsizing or abandoning their neuropsychiatric drug development program because the enormous cost of researching a drug and bringing it to the market is economically unviable when there is no assurance that the drug will be approved by the regulatory authorities, or that it will subsequently succeed.[8] Cariprazine is a recent example; the USA Food and Drug Administration acknowledged that the drug demonstrated efficacy but asked for more data on issues related to dosing and adverse effects. Generating the necessary data would be an additional financial burden with no certainty about future profitability.

With this background, we suggest an audacious idea. So far, the vast majority of recent drugs have been discovered, developed, or both discovered and developed by pharmaceutical companies in the Western world. The costs have been very high due to the higher costs of living, higher manpower and infrastructural costs and higher legal risks in the West. All these costs are far lower in developing countries. Developing countries also have a rich history of traditional medicine that can be explored for new leads. It may therefore make sense for the drug development industry to move to developing countries, lock, stock and barrel.

At present, drugs are developed in the West at formidable cost and afterwards marketed in developing countries. Under the new patent regime, generics of these cannot be marketed in developing countries until the patents expire; therefore, new drugs will be inaccessible or unaffordable to the poor across the world until the patents expire.[9] Consider the situation where the entire drug development process is shifted to developing countries. This would mean that the laboratory research as well as the Phases I, II and

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III clinical trials (and later, post marketing surveillance) could be completed at low cost for specific marketing in the countries of origin and in other participating countries. Later, Western markets can select the drugs in which they have interest and conduct local trials to meet their local regulatory requirements at a much lower risk of regulatory challenges, regulatory failures and post marketing failures.

This is a win-win situation for everybody: Costs will be low, accessibility will be high and the pharmaceutical industry will be more willing to invest in research and development initiatives instead of shutting the door on neuropsychiatric drug development. There is no need for a radical shakeup; the laboratory and clinical trial infrastructure, as well as the regulatory structure, is already in place in many developing countries, including India. With a little bit of initiative, these can be tweaked into readiness for the future.

Some Indian pharmaceutical companies have already picked up the gauntlet; Sun Pharma Advanced Research Company is working on advanced drug delivery systems and Biocon is working on oral insulin as just two examples. It is hoped that there will be major initiatives in the neuropsychiatric segment, soon.

Readers who are skeptical about whether or not this idea will work may wish to consider blonanserin, a drug that was developed in Japan, marketed in Japan and South Korea[10] and now made available in India at an affordable price. Blonanserin compares favorably in efficacy and adverse effect profile with haloperidol and risperidone.[10,11] If blonanserin can be successfully developed to the Asian markets, why not other neuropsychiatric drugs? As a side note, the decision to limit the blonanserin market to Asia was unlikely to have been preplanned. A clinical trial[12] of blonanserin was conducted in Europe and the USA with a view to obtaining approval for marketing in the Western markets. However, this development was halted by the company in October 2008 because of investigational new drug inactivation. Perhaps the company preferred to focus on the development of its newer drug, lurasidone. Perhaps the company did not want blonanserin to compete with its own newer drug. Whatever the reason, however, the message is clear: A drug can be successfully developed, trialed and marketed in an Asian market. There is recent news that blonanserin is undergoing clinical trials for potential marketing in China, as well.[11]

As a parting note: a possible way forward, at least for the moment, was outlined by McMahon and Insel:[4] the exploitation of pharmacogenomics toward personalized medicine. And afterwards, why not drugs that might represent real advances in the treatment of major mental illness, rather than merely me-too drugs? Therein lies the challenge.

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