Letter to the Editors

Time for clinical trials of epigenetic drugs in psychiatric disorders?

Jacob Peedicayil & Aniket Kumar

Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore, India

We read with great interest the Editorial by van Gerven and Cohen [1], in which they discussed the issue of the dearth of new drugs in clinical psychopharmacology despite the fact that the currently used drugs are often not effective and based on mechanisms that were largely already known in the 1970s. These mechanisms almost exclusively involve the primary neurotransmitters and their receptors. As stated by the authors, however, psychiatric disorders are complex, and cannot be explained adequately only in terms of changes in neurotransmission.

In this context, we wish to discuss the relevance of epigenetic therapy in clinical psychopharmacology. Epigenetic therapy, a new development in pharmacology, refers to the correction of epigenetic defects [2, 3]. Such defects involve changes in gene expression without changes in DNA sequence [2, 3]. They include abnormalities in patterns of DNA methylation, histone modifications and abnormalities in RNA-mediated regulation of gene expression [4]. Although there are several classes of epigenetic drugs under investigation, at present most attention is being paid to two drug classes: DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors [2, 3].

There is increasing evidence that epigenetic defects play a major role in the pathogenesis of psychiatric disorders, with some epigenetically modified genes having been implicated in the pathogenesis of these disorders [4, 5]. Interestingly, some of the genes found to be epigenetically modified in patients with psychiatric disorders code for enzymes [6] and receptors [7] involved in the activity of the primary neurotransmitters.

There is evidence suggesting that epigenetic drugs may be useful in treating psychiatric disorders. Thus, several psychotropic drugs currently in clinical use have been shown to exhibit epigenetic effects in addition to their commonly understood mechanisms of action [3]; however, epigenetic effects are not the main actions of these drugs. An example of such a drug is the mood stabilizer valproate, which in addition to its well-known actions on nerve conduction, also inhibits HDAC [2, 3]. Epigenetic drugs have also been found to be effective in preclinical

trials in the treatment of psychiatric disorders. For example, Tremolizzo *et al.* [8] showed in a methionine-induced epigenetic mouse model of schizophrenia that valproate enhanced acetylated histone 3 content, prevented methionine-induced hypermethylation of the promoter of the *RELN* gene, the gene that encodes the protein reelin, and corrected behavioural abnormalities in the mice. Kundakovic *et al.* [9] found, using cultured NT-2 neuronal precursor cells, that the DNMT inhibitors doxorubicin, azacitidine and zebularine inhibited DNMT1, leading to the activation of the expression of the *RELN* and glutamic acid decarboxylase 1 (*GAD1*) genes, both of which have been found to be epigenetically modified in postmortem brains of patients with schizophrenia and bipolar disorder [4].

To our knowledge, except for valproate, no epigenetic drug has undergone clinical trials in patients with psychiatric disorders. As the use of epigenetic drugs in patients with psychiatric disorders appears to be promising, we suggest that it is time for clinical trials of epigenetic drugs in these disorders. Epigenetic therapy may fulfil the need for newer and more effective drugs in clinical psychopharmacology.

Competing Interests

There are no competing interests to declare.

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CORRESPONDENCE

Dr Jacob Peedicayil, Department of Pharmacology and Clinical Pharmacology, Christian Medical College, Vellore 632 002, India.
Tel.: +91-416-2284237
Fax: +91-416-2284237
E-mail: jpeedi@cmcvellore.ac.in