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Viewpoint

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How Do We Re-Engage the Pharmaceutical Industry in Research on Serotonin and Psychiatric Disorders?

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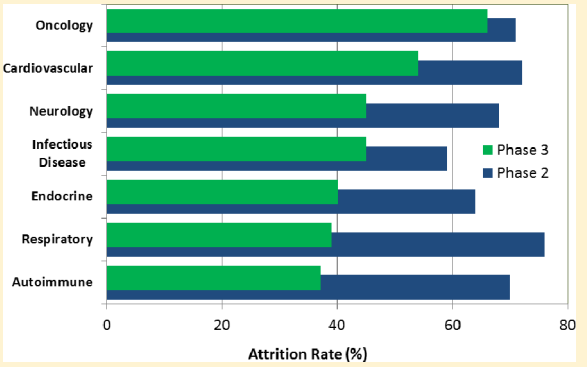
ABSTRACT: The Serotonin Club celebrated its silver jubilee in 2012 with a meeting in Montpellier, France. During the past 25 years, great advances have been made in our understanding of the pharmacology of serotonin receptors and the roles of this neurotransmitter in psychiatric disorders. Most of these advances have involved effective collaborations between academic and industrial scientists. In recent years, however, this picture has changed, as many of the major pharmaceutical companies have pulled out of in-house psychopharmacology research into the major psychiatric disorders, despite an increasing worldwide burden of these disorders and a clear need for improved treatment, particularly in terms of improved efficacy. This Viewpoint investigates the reasons for the decline in industrial involvement and makes proposals as to how future academic research on serotonin function in the brain might reawaken industry interest in serotonin-based research. Briefly, academic preclinical scientists need to alter their experimental approach to research into the psychiatric disorders. This will require a move from a single-target approach to understanding the complex neuronal pathways the cause diverse functional and behavioral outputs, using novel technological advances and the development of animal models with enhanced translational values. It is hoped that such an approach will reveal novel drug targets and thus re-engage the pharmaceutical industry in research that will result in improved human health and social well-being.



KEYWORDS: *serotonin, psychopharmacology, pharmaceutical industry, academic research, animal models, molecular imaging*

The meeting of the Serotonin Club in July 2012 in Montpellier, France celebrated 25 years since the founding of the Club by Prof. Paul Vanhoutte (cf. viewpoint by Vanhoutte, this issue). This meeting marks 63 years since Maurice Rapport published his seminal paper[1] in which he reported that the structure of serotonin was that of 5-hydroxytryptamine (5-HT). Rapport had been working at the Cleveland Clinic with Irvine H. Page, whose group had, for many years, been investigating this vasoactive substance and who had been the first to isolate it.[2] Soon after in 1952, serotonin was reported to be present in brain by John Gaddum in an oral communication to the Physiological Society, in which he also postulated that this substance might have a role as a neurotransmitter influencing mood.[3] In the intervening years, many major discoveries have been made regarding serotonin, including its involvement in the mechanism of action of antidepressants and other therapeutic drugs, and also its role in the psychoactive properties of compounds like lysergic acid diethylamide (LSD) and 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Many serotonin receptor subtypes have been identified, most of which are now known to be expressed in the brain. A substantial number of these major findings were made by past and present members of the Serotonin Club.

Despite this formidable track record of Serotonin Club members, and the pleasure of listening to first class science and reconnecting with old friends and colleagues at this meeting of the Club, there was a sense of anxiety among the psychopharmacologists present in Montpellier; all are well aware of the major challenges ahead. Many of the major pharmaceutical companies have recently closed, or are currently closing in-house psychopharmacology research on the major psychiatric disorders, namely, depression, schizophrenia, and anxiety.[4] These closures are occurring despite the fact that the burden of psychiatric illness in the world is already severe and projected to worsen in the future.[5] One of the features of serotonin research has been the productive association between academic and industrial scientists as, for example, in the discovery of receptor subtypes where research was immeasurably enhanced by novel compounds produced by pharmaceutical chemists working in industry. Any loss of research activity in industry is therefore not only going to impinge on those working in pharmaceutical companies that are closing, but also the whole of the academic research community. Why this change in attitude to psychopharmacological research in industry has occurred and how future research on serotonin

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function might reverse this disturbing trend are key questions that need to be answered.

First, why is the pharmaceutical industry pulling out of research in psychopharmacology? A major reason is undoubtedly the failure to discover new and efficacious drugs for treating psychiatric patients. We suggest that this is due to the historic nature of drug discovery in this area of medical research. The introduction of drugs to treat major psychiatric disorders was empirical, resulting primarily from clinical observations of the effects of compounds that were being used for other clinical conditions.[6] The idea that brain monoamines controlled mood became rapidly accepted. Along with further studies on the mechanism of action of antidepressant, antipsychotic, and anxiolytic drugs, considerable efforts were made to develop animal models to assist identification of novel compounds. Crucially, these animal models were said to be predictive when the existing drugs that were clinically active gave "positive" responses. The major weakness of this approach is that many of the simpler models only identified new compounds that had the same neurochemical mechanism of action as earlier drugs, thereby leading to a generation of so-called "me too" drugs, rather than the development of drugs with novel mechanisms of action.

Further honing of the discovery approach occurred when research shifted to focus on specific mechanisms or sites (receptors or transporters) of drug action to try to guide the development of new drugs with that specific mechanism. For example, the earlier tricyclic nonselective uptake inhibitors (primarily serotonin and norepinephrine reuptake inhibitors) led to the development of the serotonin-selective reuptake inhibitors (SSRIs). Similarly, the idea that the antipsychotic activity of the neuroleptics resided in their dopamine D2 receptor-selective antagonist actions resulted in numerous compounds being synthesized having this specific property. The general success of this approach enhanced the idea that there might be a single, final common mechanism responsible for the morbidity of psychiatric disorders, which was thus amenable to pharmacological intervention. If not, how otherwise can we understand the enthusiasm of industry to embrace robotics as an initial drug identification scheme, followed by testing of identified compounds in animal models?

The weakness of such ideas now seems evident when considering complex illnesses such as depression and schizophrenia, both of which are likely to result from diverse etiologies in patient populations. Morbidity is clearly going to be linked to complex neuronal pathways that induce diverse functional and behavioral outputs. This latter point is probably best exemplified by schizophrenia in which there is a triad of symptoms (positive, negative, and cognitive) not all explicable by a single neurotransmitter pathway. While selective dopamine D2 antagonists are effective in treating the positive symptoms (hallucinations, delusions, and distorted thought) of schizophrenia, they have little or no efficacy to ameliorate negative symptoms (social withdrawal) or cognitive disturbances. We suggest this may explain the fact that the most efficacious drugs for treating schizophrenia (clozapine and quetiapine, for example) are relatively nonselective in their actions at monoamine receptors.

It is also notable that the efficacy of antidepressants, most based on monoamine reuptake inhibition, has increased little in 40 years. In 1965 a Medical Research Council (UK) led trial[7] reported that imipramine had an overall 72% rate of efficacy. However, the placebo rate of improvement was 45%. These results indicated that not only did 30% of patients not improve during treatment, but also that 45% of treated patients would have improved without pharmacological intervention. This suggests a "real" efficacy of imipramine of ~30%, not a very impressive figure, and one that has improved little in the subsequent 45+ years, despite many new drugs that have been marketed. While newer antidepressants generally have fewer acute adverse effects and reduced overdose potential, their overall efficacy is still unacceptably low.[8]

Pharmaceutical companies have therefore decided they cannot justify the huge investment they have been making in CNS research given the low likelihood of success in launching a safe drug with enhanced efficacy compared to the many other drugs already on the market. However, it is interesting that similar rates of failure are seen in other therapeutic areas, which are still being fully supported by pharmaceutical industry research (Figure 1).

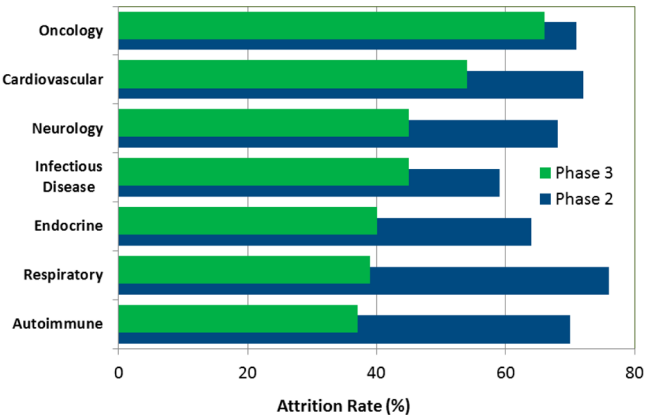

Figure 1. Drug failure rates by therapeutic area. Overall percent of failure rate at phase 2 (P2) and phase 3 (P3). Figure adapted from presentation by Dr. T. P. Blackburn, with permission.

What industry is now proposing is partnerships with small companies that have interesting lead compounds, and also to collaborate with academic scientists that have research projects considered by industry to lead to the identification of new therapeutic targets and/or novel therapeutic compounds. In this way, drug companies will share the risk of discovery and concentrate on what they do best, undertaking safety and clinical studies, and performing marketing activities.

It is this new approach to preclinical research that will be both an opportunity and a problem for scientists undertaking research on the psychopharmacology of serotonin. Obtaining funding for such studies is going to be challenging. If a research group has exciting data that look ripe for translation into a therapeutic approach, then members of industry may be amenable to establishing a partnership. However, fundamental mechanistic studies are unlikely to be funded unless commercial possibilities can be emphasized. Governmental funding (NIH, MRC) or charitable grant agencies can assist, but the current worldwide recession greatly limits the availability of such funds.

We propose that it is now vital for preclinical scientists to re-evaluate how they approach future research, both in terms of the organization and selection of questions that need to be answered. With regard to scientific questions, the emphasis in the past on single molecular targets has resulted in a mass of information on individual receptors and other molecular sites, but relatively little information as to how these various potential

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targets interact with each other to produce clinically important behavioral end points, such as emotional and cognitive processing, which are key features of mental disorders. We need to understand not just the anatomical pathways involved but also the neurochemical interactions important in the expression of behavior. To obtain this information, we need to develop more sensitive and reliable techniques for simultaneous molecular imaging of molecules and proteins (amine, amino acid, and peptide neurotransmitters, and receptor and transporter proteins, etc.) relevant to our understanding of serotonin function in the brain. In the past 15 years or so, methods such as microdialysis and voltammetry have provided us with important new information about monoamine neurotransmission, but these methods are limited by lack of speed and sensitivity (microdialysis) or are limited by the number of substances that can be detected (voltammetry). It is hoped that advances in technology will lead to the development of probes that can simultaneously monitor multiple substances at multiple sites within the brain so we can truly begin to understand neural pathways in a manner meaningful to human disorders.[9]

Returning to the organization of research, it is surely not a coincidence that the most productive period for drug discovery came in the 1960s when research groups were smaller, something the pharmaceutical industry has now recognized with its new emphasis on small groups in its own laboratories and its proposed links with small companies and university groups. Economy of scale prevents the stifling bureaucracy that has been present in industry for many years with its enthusiasm for "centers of excellence". It also used to be the case that preclinical and clinical scientists often worked closely together at the powerhouses that existed, such as the National Institutes of Health in Bethesda.[10] This meant that preclinical scientists were more informed regarding the clinical problems of psychiatric conditions. Conversely, clinicians were aware early in the discovery process of new preclinical data obtained in experimental drug investigations.

A key issue for the future of preclinical research in this field is the improvement of animal models of neuropsychiatric disorders, such that their translational value is enhanced. Interdisciplinary approaches can then lead to models that demonstrate more of the main clinical features of each disease under investigation, combined with greater understanding of the neurobiology that underlies different diseases. Steps in this direction have already occurred in the schizophrenia field with the development of models that take into account neurodevelopmental aspects combined with genetic manipulation of specific neurotransmitter systems so that models exhibit a more comprehensive profile of symptoms, including cognitive dysfunction.[11] The MATRICS initiative has also addressed this point in schizophrenia research by noting key features of this illness and proposing a new battery of animal behavioral tests to examine the different pathological features, in conjunction with improved neurodevelopmentally based animal models of the disease.[12]

Perhaps the same approach could be helpful in developing a test battery for the different behavioral domains for depression, thus affording greater insight into the dimensions of this disorder for which new pharmacological treatments may be particularly effective. However, because of the difficulties associated with measuring emotional behavior in nonprimate models, depression presents a particular challenge to those wanting to develop animal models based on the neurobiology of emotional disorders. Serotonin investigators could surely work fruitfully with clinicians and experimental psychologists to develop this approach. Preclinical scientists working more closely with clinical scientists will also be made more aware of pharmacokinetic−pharmacodynamic integration[13] and issues surrounding clinically relevant dosing. If work is being done with industry colleagues, they should also be able to obtain vital pharmacokinetic data about novel drugs and use this information appropriately.

While the foregoing does suggest real problems for preclinical and clinical experimental scientists studying major psychiatric illnesses in the next few years, both in terms of funding and experimental approaches, there are clearly great possibilities to be gained by greater understanding of the neural networks involved in complex behaviors. This in turn will reveal novel targets for the treatment of disorders that produce such heavy burdens on society, both in social and financial terms. A similar experimental approach could be adopted for disorders such as attention deficit hyperactivity disorder, autism, post-traumatic stress disorder, and drug abuse. All of these disorders show evidence of serotonergic involvement, and require further research and more effective pharmacological therapies.

It is our hope that the approaches outlined here will encourage industry to once again engage in research that will provide important prospects for the improvement of human health and social well-being.

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Notes

The authors declare no competing financial interest.

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