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THERAPIES

HEADING: Neuropsychopharmacology

Clinical research in psychopharmacology, the current situation and its perspectives. A conversation with Pierre-Michel Llorca.

Clinical research in psychopharmacology the current situation and its perspectives

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Summary

For this issue, Luc Zimmer, professor of pharmacology and chair of the Neuropsychopharmacology Committee of the French Society of Pharmacology and Therapeutics (SFPT), talked with Michel Llorca, professor of psychiatry at the Université d'Auvergne and head of a department of psychiatry at the University Hospital of Clermond-Ferrand. They discuss together the positioning of psychiatry in the neurosciences and the need to build bridges with other medical disciplines. Through examples and professional experiences, they also talk about the difficulties of developing clinical biomarkers for psychiatry and ultimately for psychopharmacology. Finally, they discuss the current difficulties facing research of drugs for psychiatry, pointing out some success stories.

KEYWORDS

Psychiatry; Pharmacology; Biomarker; Drug development

Pr. Zimmer: Pierre-Michel Llorca, what is your background and how did you get into neuropsychopharmacology?

Pr. Llorca: I completed my medical studies in Clermont-Ferrand and then I passed the psychiatric internship I chose to pursue in Marseille. During this internship, I had an early interest in cognitive-behavioural therapies that I discovered during my clinical training. I also discovered neuropsychopharmacology during my postgraduate degree in Neurosciences at the Faculty of Sciences of the University of Marseille-Lumigny. My research subject was the exploration of plasma levels of methoxy-hydroxy-phenylglycol (MHPG), a degradation metabolite of norepinephrine, in anxio-depressed subjects. This year really opened my eyes to the main concepts of biological psychiatry.

Then I spent two years at Laval University in Canada in the psychiatry department of Pr. André Villeneuve. I worked there on the topic of resistant schizophrenia. This period was a real immersion in North American clinical research, still different at this time from our practice in France. Thus, on this side of the Atlantic there were already very strong links between clinical practice and fundamental research. My first scientific paper focused on the association of adjuvant molecules such as bromocriptine, carbamazepine and cyproheptadine with neuroleptics. Despite possible pharmacological mechanisms, the clinical results were disappointing and we could not show any specific efficacy of those drugs on positive and negative symptoms [1].

Then I went back to Marseille and was involved in research on clozapine. This antipsychotic was then coming on the market in France and we confirmed its efficacy on negative symptoms with already the need to correlate its plasma levels and its tolerance [2,3].

In 1996, I returned to my native Clermont-Ferrand, where I became head of department in a private clinic that was part of a collaborative network of multicentric pharmacology studies. This gave me the opportunity to establish relationships with the academic community and in particular with Pr. Alain Eschalier who was at the Head of the Pharmacology Department at the University Hospital in Clermont-Ferrand. The latter encouraged me to continue my university curriculum with a PhD that I obtained in 2001 and then my appointment as a university hospital professor in 2002.

Clermont-Ferrand was not a university town well known for its research work in psychiatry. The key challenge for me was to structure emerging research themes. This was done by establishing scientific collaborations with the Parisian team of Pr. Marion Leboyer in the field of genetics [4], then pharmacogenetics. In this context, we have recently contributed to the hypothesis that schizophrenia may have immune-inflammatory underpinnings, possibly opening personalized treatments [5]. I have also opened psychiatry to addictology, a hospital-university discipline

recently instituted in Clermont-Ferrand [6-8]. Finally, I turned to teams of neurologists by working on the neuropsychiatric dimension of Parkinson's disease, before and after deep brain stimulation [9]. But one of the milestones of my career was the creation of the Scientific Fondation FondaMental [10] in 2007, directed by Pr. Marion Leboyer, in which I coordinate four networks of Expert Centers in France devoted to specific illnesses (bipolar disorders, schizophrenia, treatment resistant depression and autism spectrum disorder). One of the goals of this network was to built cohorts to gather clinical, neuropsychological, biological and in the next future imaging data and to create database open to researchers... It is still an undergoing project, but we have already a few scientific successes, publishing more than 100 papers in the last 6 years! Coordination is sometimes difficult but collectively we create an amazing tool for research.

Pr. Zimmer: Indeed, this a very exciting project. Finally, has the organization of research in psychiatry at your university required the development of collaborative bridges with other medical disciplines?

Prof. Llorca: Yes, absolutely. Thus, the organization of psychiatric research in Clermont-Ferrand has been built around the development of neuropsychiatric interfaces with other medical disciplines. I have always sought to enrich psychiatry and neuropsychopharmacology with other disciplines. Let's take the example of pharmacogenetics. Pharmacogenetics is part of the study of polymorphisms and their correlation with the response to antipsychotic drugs. While the concept is brilliant, it is too limited in its methodological approach. A metrological dimension was missing in the treatment of epidemiological, behavioural and neuroimaging data. We therefore sought to develop more refined but also standardized scales in order to be robust and reproducible. We cannot be satisfied with the DSM (diagnostic and statistical manual of mental disorders) which is a categorical tool but which does not allow us to evaluate clinical dimensions. An overall score overwhelms the precision of the analysis of phenotypes. The research domain criteria (RDoC) does not answer this either. In contrast to the DSM, RDoC aims to be a biologically-valid framework for understanding mental disorders. Its purpose is therefore not the same. In this case, the initial diagnosis is not central, as the approach is based on phenotype. But here again, we are talking about vast epistemological debates!

My interest is to provide tools that clinicians can use. But which clinicians are we talking about? Not so simple because a neurologist will tend to use a checklist whereas a psychiatrist will need more dimensional tools. So there is still work to be done before shared tools are available!

Pr. Zimmer: *Let's go back to psychopharmacology. You were an investigator for a significant number of research protocols for pharmaceutical companies. What is your perception of the drugs currently available in psychiatry?*

Pr. Llorca: There's a real problem with the drugs that are available. The first limitation is that many of the hypotheses underlying pathophysiology in psychiatry are built on the observations of the effects of the first psychotropic drugs (neuroleptics, ...). There is therefore a bias and a probable oversimplification. Thus, the postulates of dopaminergic involvement in schizophrenia and serotonergic involvement in depression are based on direct and indirect findings which, by force of repetition, have become real dogmas. This biological psychiatry now lacks nuances and needs to evolve. These mechanisms remain valid but are too reductionist. This being said, I do not claim to have alternative explanations.

To date, many pharmaceutical companies that have tried to explore other pharmacological avenues have failed to move to proof-of-concept in humans. I have in mind bitopertin, a glycine reuptake inhibitor, which was under development by a pharmaceutical company as an adjunct to antipsychotics for the treatment of persistent negative symptoms. It was proposed that glycine acts as a required co-agonist along with glutamate at N-methyl-D-aspartate (NMDA) receptors and dysfunction of these receptors may play a key role in the pathogenesis of schizophrenia. Therefore the modulation of glutamatergic signalling via increased concentrations of glycine may potentiate NMDA receptor function and, theoretically, improves the symptoms of schizophrenia. In a first phase II proof-of-concept study patients on bitopertin experienced a significant improvement in the change of the negative symptom factor score. Unfortunately, bitopertin failed to meet its endpoints in two phase III trials assessing its efficacy in reducing negative symptoms of schizophrenia. Research into this indication has been largely halted as a result of disappointing trial results. Was the pharmacological mechanism a false lead or was the methodology for assessing symptoms inadequate? Here again, metrology in psychiatry is crucial!

Thus, the variability of the patients recruited, whose subgroups can be revealed after the fact, remains a bias and a real methodological puzzle in psychiatric research. Current screening tools are too limited and would require more dimensional explorations.

This being said, we should not blacken the picture either! Current molecules, although improvable, still provide good services. For example, a meta-analysis by Stefan Leucht in Munich compared the

size of the therapeutic effects of molecules in the main pathologies and showed in the end that psychotropic drugs were no less effective than those in other medical fields [11].

***Pr. Zimmer:** How do you see the current therapeutic innovation in psychopharmacology? In particular, what do you think of the current enthusiasm for ketamine, an old molecule that has been totally revisited?*

Pr. Llorca: In my opinion, ketamine (or esketamine) is the only recent innovation in psychiatry. This molecule has an effect on resistant depression, with remarkably short delays of action, and on suicidal ideation. Surprisingly, the pharmaceutical company that has the license for this molecule has started on the indication of resistant depression, probably more under the guidance of its marketing department than its R&D department. Under the appearance of a very large market, and with an undeniable clinical need, this indication is very risky for phase III studies because, once again, the biomarkers are insufficient and the stratification tools insufficiently developed. Personally, I would have preferred to focus on the indication of suicidal ideation.

Another particularity of innovation in psychopharmacology is the appearance of start-ups that take risks on sometimes daring pharmacological concepts. These small companies target micro market segments such as orphan diseases. The creation of these start-ups should therefore be encouraged, but not with the sole aim of eventually being absorbed by big pharma.

The COVID crisis has also shown that the pharmaceutical industry is not an industry like any other and should be secured at the European level. It seems to me that there is still not enough joint reflection in Europe between the authorities, government agencies and the pharmaceutical industry.

The US FDA is more involved in this process. The American market is still an unavoidable route for drug R&D; the implementation of research protocols is facilitated but, surprisingly, once the molecule obtains approval, access to the North American market is more complex.

The French market remains interesting for big pharmas because, despite very controlled drug prices, it is a market to which a very large population has access, thanks to the drug reimbursement policy. But in France, the world leader in psychopharmacology at the time of Delay and Deniker, still a privileged place for research in neuropsychopharmacology?

Pr. Zimmer: We have to face the facts: no, France no longer has leadership in terms of research in neuropsychopharmacology, both at the academic and industrial levels. Indeed, there aren't many pharmaceutical manufacturers in France anymore and those that are still present invest only a little in R&D in psychiatry

Pr Llorca: We are both hospital-university professors, so we need to take an objective look at the current situation of academic research in psychiatry in France. There are only a few university hospitals that excel in psychiatric research (in any case, less than in neurology). It must also be recognised that the psychiatric community needs to recover from a gap in comparison with other biomedical communities. For too long, the French community has been impregnated by psychoanalysis, which was not favourable to the emergence of biological psychiatry. But we need both: research has to be developed in the field of psychopathology and neurosciences, and bridges have to be built. I guess that transdisciplinary approaches have to be developed! And, although the gap is narrowing, the number of young French MD/PhD psychiatrists is still too low, with insufficient teaching in clinical research among interns.

Pr Zimmer: And not enough courses in neuropsychopharmacology for young psychiatric residents... We should be inspired by some of our European neighbours!

Pr. Llorca: Absolutely. Thus, Spain has structured itself in a remarkable way with certain universities in the so-called 'psychiatric reform' that began in 1986. The main result in research was a dramatic increase in scientific productivity in the last decade among research groups, in part due to the creation of the Spanish Mental Health Network, the Centro de Investigación Biomédica en Red en el Área de Salud Mental (CIBERSAM). In Germany, although there are fewer university hospital academics with permanent positions, they have substantial financial resources that enable them to carry out high-level research, particularly with contributions in PET molecular neuroimaging. Italy has also invested a lot with the contribution of scientific societies. And I am not talking about the Nordic countries, where there are many examples of psychiatric institutions of high scientific standing!

You only have to look at the participation of these nations in the European Psychiatry Association (EPA) or in the European Collegium of Neuropsychopharmacology (ECNP) to see their investment in biological psychiatry. Saying that, I must remind that currently the President of

the EPA is Pr. Philippe Gorwood, professor of psychiatry at the Descartes University in Paris, so we can observe changes... So let be optimistic, future is still unwritten!

Pr. Zimmer: Thank you Pr. Llorca for this very interesting talk.

Disclosure of interest

Authors have no competing of interest to declare

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