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**PROGRESS IN RESEARCH AT THE CIBERSAM'S AFFECTIVE DISORDERS
PROGRAMME OF THE UNIVERSITY OF BARCELONA HOSPITAL CLINIC**

THE EUROPEAN JOURNAL OF PSYCHIATRY

Vol. 23, Supl., (174-180), 2009

Keywords: Affective disorders; Bipolar Disorders;
Unipolar depression; Neurobiology; Epidemiology;
Treatment.

Progress in research at the CIBERSAM's Affective disorders programme of the University of Barcelona Hospital Clinic

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ABSTRACT – The affective disorders programme at the University of Barcelona Hospital Clinic involves two separate subgroups according to their research target: the Unipolar Depression subgroup and the Barcelona Bipolar Disorders Programme. Both are part of the Spanish “*Centro de Investigación Biomédica En Red en Salud Mental*” (CIBERSAM), which is a Virtual Center of Network Research in Mental Health and Psychiatry, which has gathered the best research groups in Psychiatry and related disciplines in Spain. The Clinic-Affective Disorders research group has focused on the neurobiology (genetics, biomarkers, neuropsychology, neuroimaging), epidemiology (clinical subtypes, comorbidity, psychometric assessment, functionality), and treatment of bipolar and unipolar affective disorders (including pharmacological, biophysical, and psychosocial strategies). It has an outstanding and long tradition of collaborative research with national and international groups, and publishes over 60 original articles per year based on research findings, many of which have had significant impact on clinical practice.

Received 31 December 2008

Revised 12 March 2009

Accepted 12 March 2009

The CIBERSAM and the precedents

The birth, since 2008, of the Spanish “*Centro de Investigación Biomédica En Red*

en Salud Mental” (CIBERSAM), which is a Virtual Center of Network Research in Mental Health and Psychiatry, was a cornerstone in the history of Spanish research in mental disorders. The CIBERSAM has enhanced quite substantially the productivity

of the best research groups in Psychiatry and related disciplines, most of which had already been funded in 2007 by the Instituto de Salud Carlos III through the Red de trastornos afectivos y psicóticos (REM-TAP) and a few other networks on neurologic diseases, child psychosis, epidemiology, genetics, and consultation psychiatry. In the past, psychiatry research in Spain was very much dependent on individual action from specific research groups, which would look for funding from the Spanish *Fondo de Investigación Sanitaria* (FIS), foreign institutions (such as the Stanley Foundation), and the pharmaceutical industry. This fact, combined with the dearth of actual investment, had a negative impact on the strategy of the groups that were struggling to do high-quality research on a long-term basis. The CIBERSAM was born as a new era in Mental Health research in Spain, providing unprecedented long-term funding to the best research groups and enhancing translational, collaborative research across the country. Moreover, all the process was made under the highest transparency, fair competition, and peer-review.

The affective disorders programme at the University of Barcelona Hospital Clinic which I have the honour to coordinate involves two separate subgroups according to their research target: the Unipolar Depression subgroup and the Barcelona Bipolar Disorders Programme.

The Unipolar Depression Subgroup

This subgroup is led by Cristóbal Gastó, Chair of Psychiatry at the University of Barcelona, and includes Jordi Blanch, Teodor Marcos, Víctor Navarro, and recently Rocío Martín-Santos. They have been ex-

tremely successful in investigating genetic polymorphisms and their relationship to therapeutic response¹, the role of serotonergic receptors in depression and its treatment², the specific issues related to depression in the elderly³, and cognition⁴. The group is involved in several CIBERSAM-funded multicenter projects, such as the DEPRES study, and collaborates on a long-term basis with other CIBERSAM groups such as the one led by Lourdes Fañanás.

The Bipolar Disorder Subgroup

This subgroup involves most members of the Barcelona Bipolar Disorder Programme at the University of Barcelona Hospital Clinic (BDP). The BDP integrates clinical care, education, research and management devoted to provide excellence in care and knowledge on bipolar disorder, and it belongs to 3 institutions: the Hospital Clinic, the University of Barcelona, and the *Institut d'Investigació Biomèdica August Pi i Sunyer*, (IDIBAPS).

The functional unit that provides clinical care to patients with bipolar disorder is the Bipolar Disorder Unit at the Hospital Clinic, which delivers specialized care to bipolar patients attending the hospital regardless of their condition as in- or out-patients. Bipolar outpatients may come for specialized secondary care (Mental Health Center) or for tertiary care as reference center for particularly difficult-to-treat cases. I am the director of the Programme and I coordinate a large multidisciplinary team, which involves excellent mental health professionals and researchers such as Antoni Benabarre, Mar Bonín, Francesc Colom, Mercè Comes, Núria Cruz, Claire Daban, Carolina Franco, José Manuel Goikolea, Anabel Martínez-Arán, Isabella Pacchiarotti, María Reinas, Adriane Rosa, José Sánchez-Moreno, Carla Torrent,

and Marc Valentí. Several professionals collaborate with the team, including young investigators, fellows and residents, such as Piero Castro, Andrea Murru, Lorenzo Mazzarini, Alessandra Nívoli and Ekaterina Popova, among other.

The BDP research has focused on the neurobiology (genetics, biomarkers, neuropsychology, neuroimaging), epidemiology (clinical subtypes, comorbidity, psychometric assessment, functionality), and treatment of bipolar illness (including pharmacological, biophysical, and psychosocial strategies). It has an outstanding and long tradition of collaborative research with national and international groups, departing from the premise that true science has no geographical or cultural borders, and that little can be done separately. The CIBERSAM has provided further impulse to collaborative projects, yielding a growing number of multi-authored scientific publications involving two or even more groups within the CIBERSAM and beyond. Special mention is deserved for the long-standing collaboration with the CIBERSAM's Valencia-Alicante group (led by Rafael Tabarés), Vitoria (Ana González-Pinto), Madrid (José Luís Ayuso), Sant Joan de Déu (Josep María Haro), and several more that are currently ongoing.

Some of the most relevant BDP output in 2008, just after one year since the start of the CIBERSAM, include, in the neurobiological arena: the development of a model of allostatic load for bipolar disorder⁵, the replication of genetic findings involving specific mutations in bipolar disorder and schizophrenia⁶, cross-sectional⁷⁻⁹ and longitudinal¹⁰⁻¹² neurocognitive studies indicating long-term persistence of cognitive deficits, even during remission, and innovation in brain neuroimaging quantification techniques¹³. In the area of epidemiology, our group has developed strategies to improve the screening and early detection of bipolar disorder in depressed patients, the as-

essment of subclinical symptoms¹⁵ and depression subtypes¹⁶, and comorbidity¹⁷⁻¹⁸; furthermore, we have conducted studies on psychosocial adjustment and functional outcome¹⁹ and innovative proposals related to the forthcoming classifications of mental disorders, such as the DSM-V²⁰⁻²². Innovation has been further fostered through the development, adaptation, and validation of several psychometric tools aimed at diagnostic screening²³, neuropsychological assessment²⁴, severity rating²⁵, and evaluation of comorbidity²⁶. Our group has been particularly active in the publication of international consensus documents for the diagnosis, cognitive assessment, follow-up and treatment of people with bipolar disorder²⁷⁻³³. Finally, in 2008 our group has made important contributions to the progress in the treatment of bipolar disorder³⁴⁻⁴¹, including a better knowledge of the efficacy and safety profile of traditional therapies such as lithium⁴², and modern strategies such as the use of long-acting injectable risperidone in difficult-to-treat and poorly adherent patients⁴³. Several pivotal randomized clinical trials were conducted and published this year, allowing the registration of new indications for drugs as aripiprazole⁴⁴, quetiapine^{45,46}, and ziprasidone⁴⁷, and several more, not necessarily sponsored by the pharmaceutical industry, provided relevant input on the potential role of oxcarbazepine⁴⁸ and amisulpride⁴⁹; a third group of trials has yielded substantial information on treatment response in specific clinical subgroups⁵⁰⁻⁵¹. The BDP prioritizes research upcoming from the clinical arena, and although basic and translational research are seen as crucial, and methodology is given the greatest attention, observational studies are considered highly valuable as well⁵²⁻⁵⁶. Such studies lack the rigour of placebo-controlled, randomized trials, but they have greater external validity and ecological value. One of them is the European study called EMBLEM. The contribution of

the BDP to bipolar therapeutics is not limited to pharmacological treatment, but actually involves a great deal of psychotherapy research, including the empirical testing of innovative approaches such as group psychoeducation, (with the first report on psychoeducation for bipolar II disorder)⁵⁷, family psychoeducation⁵⁸, and biophysical treatments, such as vagus nerve stimulation⁵⁹ and the traditional electroconvulsive therapy⁶⁰. Our group has also made relevant contributions to research methodology^{61,62}.

Ongoing and future projects

The main output from the Affective Disorders Program at the University of Barcelona Hospital Clinic after the birth of the CIBERSAM has been summarized in the preceding pages, but there is evidently a great deal of ongoing research that may yield further publications, patents and innovation within the forthcoming years. Some of those involve a large, multicenter study on first-episode psychosis (including affective psychoses), the clinical trial on treatment-resistant unipolar depression named DEPRES, a large, innovative, multicenter trial involving 10 groups from the CIBERSAM on the efficacy of cognitive rehabilitation in bipolar disorder, a translational study on molecular biomarkers in collaboration with the Vitoria group, and several psychometric projects on the validity of the Functioning Assessment Short Test (FAST) subscales and the predictive validity for weight gain of the Barcelona Bipolar Eating Disorder Scale (BEDS). Among the non-collaborative projects, there is one on individual neurocognitive rehabilitation (funded by the *Fondo de Investigación Sanitaria* with Anabel Martínez-Arán as principal investigator), another one on biomarkers for treat-

ment response to psychoeducation, led by Francesc Colom, a third one on genetic polymorphisms and lithium response by Antoni Benabarre, and another one on long-term efficacy of electroconvulsive therapy, by José Manuel Goikolea, among other. The recent finalization of a large FIS project, linked to the European study named MHADIE, in cooperation with the group from the Hospital de La Princesa in Madrid, may produce a large number of publications in the nearest future. Moreover, international collaboration may be substantially fostered by means of the ENBREC project, of which I am the principal investigator in Spain. The ENBREC (European Network of Bipolar Expert Centres) is a 7th-Framework-European-Programme funded project that aims at developing networks of networks for bipolar disorder research in Europe. The ENBREC project has also received funding and support from the European College of Neuropsychopharmacology (ECNP).

Conclusions

The Affective Disorders Program at the University of Barcelona Hospital Clinic is one of the most active and productive teams of the CIBERSAM and conducts high-quality research in the fields of unipolar depression and bipolar disorder with a strong collaborative, multidisciplinary, translational, and innovative emphasis. During the short period of a year since the birth of the CIBERSAM it has been already able to generate over 60 high-impact publications and over 1 million Euro additional funding. This is a tangible and unequivocal proof of the success of the CIBERSAM and of the quality and productivity of Spanish Psychiatry when enough funding and resources are provided. In the near future, the CIBERSAM may expand its

research activity and networking over Europe through networks of networks, fostering its capacity to develop further large, multisite collaborative international projects for a better use of research resources beyond local policies, as proven by the ENBREC project in the specific case of bipolar disorder. Hopefully this will be a foundational item in the agenda of decision-makers on European and international research on Mental Health.

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