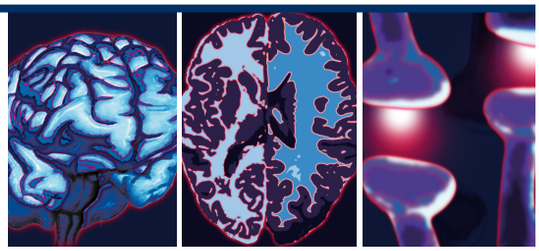

State-of-the-art research and clinical updates on mood and anxiety disorders

Xenia Gonda & Zoltan Rihmer*

11th International Forum on Mood and Anxiety Disorders, Budapest, Hungary, 9–11 November 2011

In November 2011, experts from around the world gathered in Budapest, Hungary, for the 11th International Forum on Mood and Anxiety Disorders, where several lectures were presented, addressing the most contemporary fields and clinical as well as research topics. In this article, we aimed to select the most important lectures from the various symposia and presentations in order to give a balanced overview of the results presented and questions raised during this meeting.

The 11th International Forum on Mood and Anxiety Disorders (IFMAD) was held in the castle district of Budapest (Hungary) at Hotel Hilton between 9 and 11 November 2011, with over 600 participants representing 48 countries. In spite of the warm mid-November weather and the historical location, the symposia were well attended, and vivid discussions developed following the presentations. The aim of the IFMAD congress was to increase awareness concerning the latest innovations and state-of-the-art achievements of research in mood and anxiety disorders and promote the exchange of ideas within the global psychiatric community.

There were several important and thought-provoking lectures during the meeting that were organized into several symposia, presented and chaired by the most renowned and respected experts in the field. One of the symposia was dedicated to discussing the reasons behind the decreasing number of newly introduced psychotropic medications, which has raised general concern internationally. Anders Gersel Pedersen (Lundbeck, Denmark) in his speech 'Economic barriers to developing new treatments' described the social and economic burden of CNS illnesses, and contrasted the costs of treating these disorders with the unmet medical needs (i.e., those aspects of these disorders current medications cannot address). CNS pharmacological and pharmaceutical research, however, faces more and more difficult challenges in the clinical phases of drug development compared with other fields, and the picture is further complicated by legal and regulatory obstacles. Pedersen proposed a new economic risk-sharing model to facilitate drug innovation in CNS disorders. Stuart Montgomery (Imperial College London, UK) spoke about the 'Sunset on new psychotropics in Europe', suggesting that tougher regulations for licensing new psychiatric medications and stricter criteria for their social insurance-based reimbursement in EU countries compared with medications for

Department of Clinical & Theoretical Mental Health, Semmelweis University, Budapest, Hungary
*Author for correspondence: rihmerz@kut.sote.hu

Future Medicine part of fsg

other illnesses indicate a prejudice and discrimination against psychiatric patients in spite of their suffering. These obstacles not only hinder patients' proper treatment, but also have a negative effect on the viability of developing new treatments, since, due to delays caused by difficulties in the licensing process, EU citizens often have access to treatments only when they are already off-patent, which have led pharmaceutical companies to close their neuroscience research centers in the EU and withdraw from developing psychiatric medications for the EU market, leaving European psychiatric patients with fewer options for new treatments for their illness.

There were also interesting and important talks concerning the advances in the therapy of treatment resistance. Alessandro Serretti (University of Bologna, Italy) talked about the possibilities of utilizing personalized gene-targeted therapy in treatment-resistant depression, which is a crucial question, since nearly 60% of depressive patients do not reach remission during pharmacotherapy and genetic factors account for approximately 50% of the antidepressant response. There are several gene polymorphisms that can be considered when determining what genes should be included in patient genetic profiling for antidepressant response, including the *5-HTTLPR* polymorphism and other genes encoding serotonergic receptors and enzymes playing a role in monoamine metabolism, as well as newly emerging candidate genes such as *Gβ3*, *FKBP5* or *GSK-3*β, and genome-wide scanning approaches and multisite drug studies also report new possible candidate genes. Genetics, however, was not able to predict antidepressant response on the individual level so far. Zoltan Rihmer (Semmelweis University, Hungary), in his speech on 'Antidepressant resistance in unipolar and bipolar depression', emphasized that in most cases, resistance to antidepressant treatment reflects the heterogenous nature of depressive disorders, as well as indicating the importance of better understanding and distinguishing between different subtypes of depression (since a particular medication may only be effective in certain subtypes). One of the most common causes of antidepressant resistance in unipolar major depression is, however, the subthreshold or unrecognized bipolar nature of the depressive episode, where antidepressant monotherapy is likely to induce hypomanic switches or generate mixed states, worsening the symptoms. In her presentation, Naomi A Fineberg (Hertfordshire Partnership NHS Foundation Trust, UK) outlined the available treatment strategies in order to help patients with treatment-resistant obsessive–compulsive disorder (OCD) by critically evaluating the effectiveness of first-line treatments, the duration of treatment attempts and management of treatment-resistant OCD. While a substantial proportion of patients fail to respond to selective serotonin-reuptake inhibitors, they may benefit from such strategies as dose elevation or adjunctive antipsychotics, while waiting for the latest results concerning some newer and promising compounds, such as specific and selective serotonin receptor ligands or agents targeting other neurotransmitter systems, including the opiate and glutamatergic pathways, which may be relevant in OCD treatment. David Baldwin (University of Southampton, UK), in his speech about 'Recent advances in treatment-resistant generalized anxiety disorder', emphasized the lack of recognition and treatment for those patients who could indeed benefit most from appropriate therapy, while other patients receive unnecessary or inappropriate interventions. Response rates in generalized anxiety disorder patients are disappointing in spite of first-line treatment with selective serotonin-reuptake inhibitors, serotonin- and norepinephrine-reuptake inhibitors or pregabalin, and there is a lack of studies concerning further options in these patients, although antipsychotics are a promising option.

The importance and future of the monoamine hypothesis in drug development was debated during a very vivid and thought-provoking symposium led by Ted Dinan (University College Cork, Ireland), arguing that the monoamine hypothesis is dead, and Mike Briley (NeuroBiz Consulting and Communication, France), outlining evidence against it. The results of nearly 50 years of the monoamine-centered approach in the research for an effective treatment for psychiatric and especially affective disorders indicate that drugs exclusively affecting the monoaminergic systems offer no significant improvements in terms of efficacy, suggesting that this line of research is a dead-end street. One possible error leading to the overevaluation of the monoaminergic system in the background of mood disorders is relying too widely on rodents, whose brain contains significantly more monoaminergic neurons compared with humans; therefore, this approach oversimplifies the complexity of the involvement of the human nervous system in major depression. There are newer strategies in antidepressive drug development, focusing on mechanisms related to stress or proinflammatory citokines, changes in trophic factors or miRNAs or the melatonergic system. On the other hand, although monoamine modulation was never claimed to be the only step in antidepressant action, it obviously seems to be an integral part of all forms of effective antidepressant therapies, and monoamines seem to regulate and act as the final common pathway in the action of several other neurotransmission systems. New antidepressive mechanisms, such as those involving neurogenesis and central inflammatory reactions, as well as light therapy and physical exercise, also indirectly influence the monoamine systems and may exert their action due to this biochemical cooperation. Therefore, the monoamine theory is not dead at all, but should be viewed from a broader perspective, incorporating those mechanisms that also act by indirectly modulating the monoamine systems. In another symposium, Pierre Blier (University of Ottawa, Canada) also stressed "The clinical importance of monoamine interactions in antidepressant therapy." The three brain monoaminergic systems are in a reciprocal interaction regulating and modulating each other's function, from which it follows that if we pharmacologically influence only one of these neuronal elements, it can lead to distant negative or positive consequences in the other two elements, which should be taken into account. This is especially true of dual-action (serotonin- and norepinephrine-reuptake inhibitor) antidepressants, which inhibit the two components with differing efficacy, making it even

more difficult to predict overall effects in the three monoaminergic systems. In this context, Blier emphasized the positive actions of milnacipran, which, unlike the two other serotonin- and norepinephrine-reuptake inhibitors duloxetine and venlafaxine, exerts a stronger action on the norepinephrine system compared with the serotonergic neurotransmission, leading to fewer side effects such as nausea or sexual dysfunction, as well as less discontinuation symptoms, but maintained enough efficacy concerning its serotonergic effects to have a therapeutic effect in fibromyalgia.

One of the hot-topic lectures by Ruth Baruch (East General Hospital, Canada) discussed whether branded and generic medications are interchangeable, which is indeed a very important question as the price of original medication exceeds those of generics by far, and the increasing opportunities and need for treatment of psychiatric disorders put an ever-increasing economic burden on social insurance. Due to the lower price, most insurance providers favor generic medications as part of a cost-containment strategy; however, in opposition to these purely economy-based decisions, there may be other aspects to consider when choosing between branded and generic products, which basically concern efficacy and the wellbeing of patients. Although regulations contain similar requirements for originals and generics, and the approval of a generic medication is based on strict measures of bioequivalence, the standards employed may not fully ensure that generics have equivalent efficacy and safety. Therefore, differences in effectiveness and adverse effects, adherence and symptom exacerbation should all be taken into account, thus choosing between originals and generics goes beyond simply considering costs, and so the clinician should always be the one having the final say in the matter. Therefore, the issue of clinical equivalence and interchangeability of original and generic formulations remains controversial, and if generics are less efficacious or cause more adverse effects, then they may not lead to cost saving at all.

Mood and anxiety disorders put an increasing burden on patients and the whole of society as well, and there is an impressive amount of research underway in this field, complemented by an ever-expanding amount of evidence from clinical experience. Opportunities for sharing these latest results and developments in order to improve care of our patients are crucial and unique.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.