

# CINP DAILY NEWS

THE OFFICIAL NEWSPAPER OF THE 2019 CINP INTERNATIONAL MEETING

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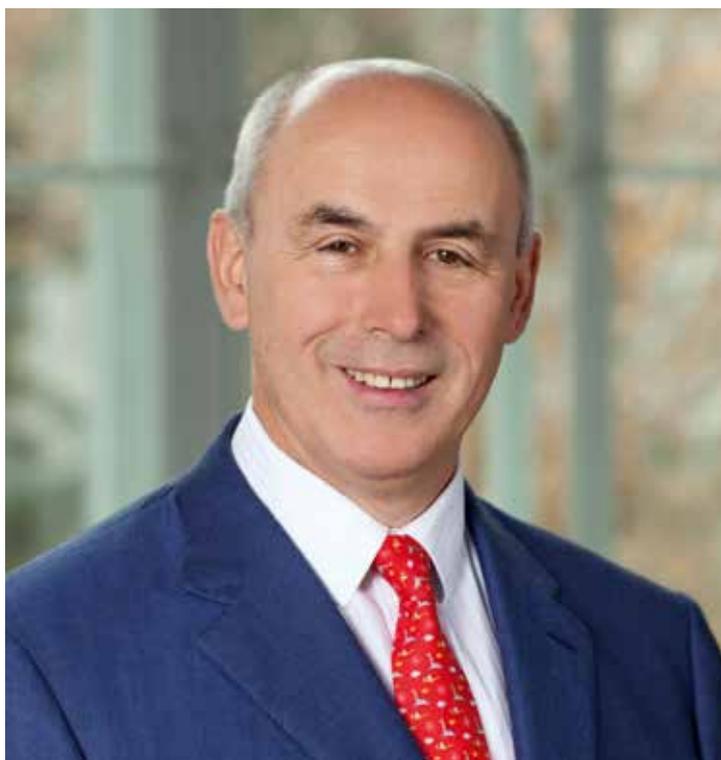
## WELCOME TO ATHENS

Esteemed colleagues,  
Welcome to the CINP 2019 International Meeting on 'Breakthroughs and Controversies in Mood, Psychosis, Schizophrenia, ADHD, and Insomnia'.

It is our great pleasure to have you with us here in the noble and historic city of Athens, Greece.

As promised, the programme of the CINP 2019 International Meeting expands on the 2017 Prague meeting, as well as on aspects from our 2018 Vienna Congress, and we have taken great care to develop the programme to bring you the newest developments in the wider fields of psychiatry and psychopharmacology.

We are proud to see a great number of delegates from all corners of the world, with a particular emphasis on delegates from the Southern European region. The diversity of our delegates again showcases the immense range of skills, backgrounds and fields of work of our membership around the world. It is indeed a true pleasure to witness the coming



together of such a truly international group of professionals, sharing their knowledge and exchanging new ideas.

Personally, as the current CINP President, I am certain that I speak on behalf of the entire leadership of CINP that we hope you will get the most out of this meeting for yourselves, your organisations and your work from this meeting. We do very much encourage you to share your ideas and engage both on-site as well as online with each other and with us, as friends and colleagues, to continue building our international community, move forward the research and education of psychopharmacology and increase our professional interaction.

Please enjoy Athens, enjoy the CINP 2019 International Meeting, and – very importantly – yourselves. I look forward to meeting with as many of you as possible during the coming days.

**Professor Siegfried Kasper**  
President of CINP (2018-2020)

### SYMPOSIUM

Breakthroughs and controversies in psychosis **Olympia Hall Thursday 13:00-14:30**

## Use and usefulness: Addressing recent controversies in antipsychotics in schizophrenia

This afternoon's symposium on breakthroughs and controversies in psychosis sees a discussion of controversies in the literature surrounding antipsychotic treatment, presented by Konstantinos Fountoulakis (Athens, Greece).

This talk accompanies a soon to be published manuscript by the joint workgroup of the World Psychiatry Association (WPA) and CINP, which provides an up to date review of relevant literature

*"From time to time, mistruths arise concerning the usefulness of psychotropic medication."*

Konstantinos Fountoulakis

and hence a consensus on the usefulness of antipsychotics, their limitations and potential dangers in the treatment of schizophrenia. In doing so, the authors establish a list of issues that have been raised

during the last few years in the frame of the debate on antipsychotics and articulate pro and con arguments on these issues.

In conversation with *CINP Daily News*, Professor

Fountoulakis explained that controversies surrounding treatment strategies are not new. "From time to time, mistruths arise concerning the usefulness of psychotropic medication," he said. "In 2008, for example, there was a controversy on antidepressants. This controversy ceased recently, having lasted almost ten years. This was in spite of the fact that all the data were positive for antidepressants, and in spite of the fact that all metaanalyses since

the beginning had shown the same thing."

These controversies – triggered by the disturbing possibility that some antidepressant medications may be linked with increased suicidal thoughts (but not deaths) in some patients – were described by Möller (2009)<sup>1</sup>. More recently, comprehensive reviews, such as that of Cipriani et al (2018)<sup>2</sup>, have significantly quelled controversy both in clinical and

*Continued on page 2*

## SYMPOSIUM

Breakthroughs and controversies in psychosis **Olympia Hall** Thursday **13:00-14:30**

# Use and usefulness: Addressing recent controversies in antipsychotics in schizophrenia

Continued from page 1  
public spheres.

“Now, there is a debate concerning the usefulness of antipsychotics in long term use,” continued Professor Fountoulakis. “And again, it is not really a matter of the scientific data.

“The problem is that a lot of people are very negativistic in principle concerning the use of medication for the treatment of mental disorders, questioning it on the basis of any small dark corner and uncharted area they can find. And in medicine, you can find many such areas. But these are the exception rather than the rule.

“You cannot reject the main conclusion on the basis of secondary and inferior problematic details. Yes, there are problematic details. But the general picture is that antipsychotics are efficacious during the acute phase.

Also, if you don't continue treatment with medication for several years, you have a higher relapse rate.”

The objections voiced against the use of antipsychotics are encapsulated by a 2015 Maudsley debate, in which it is argued that their benefits are overstated in the literature, with minimal clinically relevant effects and long term harm<sup>3</sup>. The validity of long term maintenance treatment has also been questioned amid findings such as the association of reduction of brain volume and increased risk of physical comorbidity<sup>4</sup>.

Professor Fountoulakis commented that a number of issues have persisted in recent years in this field, including knowledge gaps and difficulties in interpreting the findings of existing trials. These issues stem in part from the fact that mental disorders in general – includ-

ing schizophrenia – are possibly heterogeneous, with a number of conceptual issues arising from this.

“For example, there is a difference in the definition of

DSM, you need six months. This is a large difference.

“The ICD definition is over-inclusive and so includes cases that are very benign, which have a very good

are clear: you need long-term antipsychotic treatment.”

Efforts to pin down clinical definitions, metabolic markers, and imaging correlates that might characterise the heterogeneity of the disorder are ongoing<sup>5,7</sup>. A key knowledge gap remains, however, in the lack of randomised data on the longer term efficacy and safety of antipsychotic use. But such data are impossible to obtain, simply because patients cannot be kept under placebo for several years.

The nature and quality of long term data was recently discussed by Correll et al (2018). The authors observe that longer studies are at greater risk of accumulating systematic errors over time, leading to biased results. In addition, the longer the study, the less there is control over environmental influences. Any non-randomised study

*“If you have an established diagnosis of schizophrenia, then the data are clear: you need long-term antipsychotic treatment.”*

Konstantinos Fountoulakis

schizophrenia between the International Classification of Diseases (ICD; the classification system of the World Health Organization) and the Diagnostic and Statistical Manual of Mental Disorders (DSM; of the American Psychiatric Association),” he said. “In the WHO definition, schizophrenia is any non-affective psychosis that lasts more than four weeks. In the

outcome anyway. For several years, these patients might be doing very well at low doses. But they are not patients with schizophrenia in the way that we perceive the condition, in terms of research and in terms of DSM.

“So there are conceptual grey zones that fuel this debate. But if you have an established diagnosis of schizophrenia, then the data

## CINP Daily News

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### Programme: Thursday 3 October

**08:30** 08:30 - 10:00

**09:00** Welcome & Keynote Lecture

**09:30** Rapid acting antidepressants: opportunities and mechanisms

John H. Krystal

**10:00** 10:00 - 10:30 Coffee Break / Showcase Presentation by Sage

**10:30** 10:30 - 12:00

**11:00** Symposium Breakthroughs and controversies in mood disorders

**11:30** Francesc Artigas,  
Alessandro Serretti,  
Carlos Zarate

**12:00**

**12:30** 12:00 - 13:30

**13:00** Lunch / Poster Viewing

**13:30**

**14:00** 13:30 - 15:00

**14:30** Symposium  
Breakthroughs and controversies in psychosis  
Carol Tamminga,  
Konstantinos Fountoulakis,  
Shih-Ku Lin

**15:00**

**15:30** 15:00 - 15:30 Coffee Break / Showcase Presentation by Saladax Biomedical

**16:00** 16:30 - 17:00

**16:30** Guided Poster Session

**17:00**

**17:30** 17:00-18:00

**18:00** Meeting of Ambassadors and Corresponding Societies

**10:30 - 12:00**

**Young Scientist Forum**

John H. Krystal  
Joseph Zohar

**10:30 - 12:00**

**Meet the Expert**

Alan Frazer

**13:30 - 15:00**

**Workshop**  
NIH / NIMH

**13:30 - 15:00**

**Meet the Expert**

Sponsored by Janssen

is prone to difficulties in interpretation due to the role of unknown confounds and reverse causation.<sup>8</sup>

Elaborating on such impediments to answering outstanding questions of antipsychotic medication, Professor Fountoulakis explained that a fundamental difference between psychiatry and the rest of medicine lies in the absence of any biological markers: “When you study, for example, diabetes mellitus, in a long term study you just need to monitor blood sugar. It is easy and straightforward. Also, in diabetes mellitus you have zero placebo effect. But in schizophrenia we don’t have such biological markers, so you must rely on the clinical picture. Also, you have a significant placebo effect.

“Placebo is very complex: it includes the natural fluctuation of the illness (for some periods the person is okay, while in other periods their schizophrenia is exacerbated). You also have some psychological effects, and the effects of adverse events. A lot of things contribute to what we call the placebo effect, which is not present in many other conditions in medicine. This is a problem, because you cannot monitor the effect of a drug without a placebo.

“All these problems boil down to the need for a placebo controlled trial. But you cannot utilise placebo controlled trials for three years. Based on this, you can only do observational studies – very careful observational studies – and you need very thorough and very well conducted analysis in the extraction of conclusions.”

This is precisely what the WPA/CINP joint workgroup achieved in their recent work. “We are absolutely certain that up to three years antipsy-

chotics are absolutely necessary,” summarised Professor Fountoulakis. “Until we have some biological markers available, we will never be 100% sure about the long term need. Probably, there will be a minority of patients who do not need medication (about 5%), but it is impossible to identify them a priori.

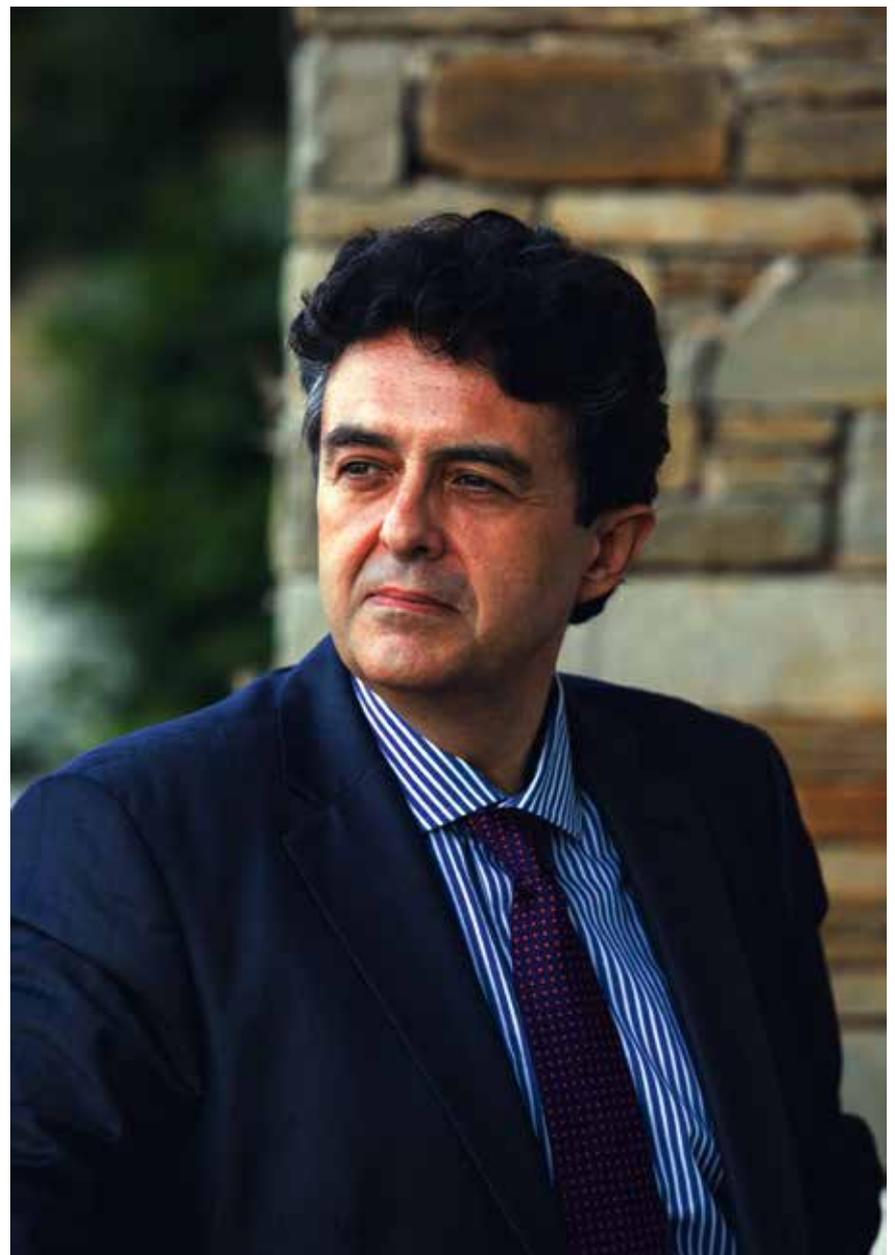
“Another issue with mental disorders which is not an issue in, for example, diabetes mellitus, is that a lot of patients do not want and do not take medication. They don’t wish to. Diabetic patients, while they might forget to take their medication from time to time, want to take their medication. A large proportion of psychotic patients (and we don’t know exactly how many, but it is probably more than 30%) do not want to take any medication at all, for ideological or personal reasons. In general, it is a riddle – a Gordian knot – that is very difficult to resolve.

Addressing the drivers for the emergence of the controversy around the use of antipsychotic medication in schizophrenia, Professor Fountoulakis cited our current inability to distinguish those patients most likely to benefit from long term medication, as well as the fact that currently available medications do not satisfactorily restore loss of functional

*“We do have agents that work...But they are not as good as we would like them to be.”*

Konstantinos Fountoulakis

deficits and return patients to work and community life. “Currently, a minority of patients seem to respond adequately, and very few have recovery,” he said. “So it is not



even a half-filled glass. It is less than half-filled.”

In his concluding statement, Professor Fountoulakis stressed that we must find credence in a nuanced perspective given the evidence

at hand: “If you take a Manichaistic approach, one view is that antipsychotics do not work – that they have some sort of statistical efficacy but that they do not have any real meaningful worthwhile efficacy. The opposite view is that

we have perfect drugs that change people’s lives radically. It is too black-and-white if you follow this approach. This is not exactly what reality is. The reality is that we

do have agents that work. We need these agents, because without them people will deteriorate faster. But they are not as good as we would like them to be.”

“Breakthroughs and controversies in psychosis” takes place from 13:30 to 15:00 this afternoon.

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## MEET THE EXPERT

60 years of antidepressants - where are we now? **Attica Hall** Thursday 10:30 - 12:00

# 60 years of antidepressants: Where are we now?



Alan Frazer with fellow faculty member Flavia Carreno

Alan Frazer (UT Health San Antonio, USA) delivers a lecture on the past sixty years of antidepressants during today's Meet the Expert session.

In taking audiences through the history of antidepressant pharmacotherapy, Professor Frazer will highlight key developments that have improved, for example, long-term compliance. He will also discuss where there is room for improvement: how new advances, such as ketamine, represent an important lead for developing even better compounds that carry fewer side effects.

The 1960s yielded the discovery of the first antidepressants – the tricyclics and monoamine oxidase inhibitors (MAOis). Subsequent decades were spent characterising their efficacy, side effects and appropriate usage. Research into their biological basis also prompted interest in the biogenic amine systems, leading to the monoamine hypotheses of depression.

But these initial hypotheses were probably simplistic, as Professor Frazer explained during an interview

with *CINP Daily News*: “There is a logical fallacy in thinking that, if a drug stimulates this, then the disease might be due to the absence of this. That is often not the case. But it at least formulated a way to do research into people with depression and to study what the biologic abnormalities might be. To some extent, that type of research occurs even today, but it is much less so than in the 1970s and 1980s.”

The benefits of tricyclics were tied up with numerous side effects, as well as their lethal dose being relatively low compared to their therapeutic doses. These issues affected both adherence and associated mortality. Then, in the 1970s and 1980s, selective serotonin reuptake inhibitors (SSRIs) emerged.

“The real question is, are we any further along clinically than we were when we started, in spite of knowing a lot more about brain function? I would conclude that SSRIs have been much better than the original drugs, but only because of side effects, not because of efficacy.

“The side effect issue is very important though, because we now know that depression is a recurrent illness in many patients. You want to keep on antidepressants those who

are likely to relapse and have recurrences for a long period of time. It was difficult to do that with the tricyclics because of the side effect profile. Also, you could kill yourself with tricyclics, and people did because they were depressed or suicidal, and you were giving them a means to kill themselves. With the SSRIs this occurs to a much lesser extent.”

*“SSRIs have been much better than the original drugs, but only because of side effects, not because of efficacy.”*

Alan Frazer

Summarising the changes in prescribing habits that have come with refinements in knowledge, Professor Frazer cited work in the late 1980s and onwards showing that a depressive episode is as likely to be isolated as it is to recur over an individual's lifetime. When recurrences were observed, it was found that if

patients with a history of at least three depressive episodes were kept on imipramine (the original tricyclic antidepressant), they were much less likely to relapse or have recurrences of their illness. This formed the basis of the long-term maintenance approach. “Now, I would say that if someone comes in with recurrent depressive episodes, you are going to keep them on the SSRI on which their acute depressive episode improved,” said Professor Frazer. “And they are likely to be more compliant with the SSRIs than with the tricyclics.”

Professor Frazer will also examine the era of personalised medicine and efforts in psychiatry research to meet the call for biomarkers to inform clinical decision-making. “The bottom line, as far as I am concerned, is that although this is a valid area for research little to nothing has emerged as of yet that is useful clinically. There is nothing that we can take from blood or any other place that tells us whether you are likely to respond to a specific drug or not.”

A real hindrance facing research, he added, is the use of diagnostic schema in study design. This is now being addressed with initiatives such as the Research Domain Criteria (RDoC), which aim to reclassify psy-

chopathology in terms of dimensions of observable behaviour that can be correlated with neurobiological markers – rather than traditional clinical diagnoses, which represent more of a symptomatic portmanteau. This, said Professor Frazer, may influence the process of conducting clinical trials by targeting specific behavioural dimensions and hence reducing the heterogeneity among subject groups.

Asked how new schema such as RDoC are likely to influence clinical diagnostics of the future, he commented: “There is no doubt that our diagnoses have no biology associated with them. They were not developed based on biological principles. Now, when you have very heterogeneous diseases, it is not surprising that when people start to talk about biological circuits involved in psychiatric disorders they will talk about the frontal cortex, amygdala, the hippocampus – as is the case in panic disorder, depression, mania, schizophrenia, etc. There may be differences in aspects of the circuits, but they are the same circuits. A lot of the comorbidity that comes with psychiatric diagnosis is because of the tremendous overlap in symptomatology.

“I think I have some idea of the biology underlying sleep, underlying eating, underlying even certain types

of cognitive processes such as memory. I even have some understanding of aspects of mood. But if you put them all together, and you try to ask, ‘what is the biology of depression?’ Well, there are a lot of different biologies.

“I agree that clinicians may not be all that excited about that. It could be a twenty-year process that allows us to come up with a better diagnostic scheme, which really tells us that it is

*“Our diagnoses, and the way we carry out clinical trials, have hindered our ability to find better drugs.”*

Alan Frazer

more likely that this patient is going to respond to this or that drug. That is the goal. We are not there yet. But our diagnoses, and the way we carry out clinical trials, have hindered our ability to find better drugs.”

He further stressed that there remain reasons to be positive, despite the obstacles facing the field. The ef-

ficacy of many pharmacological treatments for major depressive disorder has recently been demonstrated in a network meta-analysis by Cipriani et al (2018)<sup>1</sup>. And in 2012, Leucht et al demonstrated that drugs throughout medicine are as moderately efficacious as those used in the field of psychiatry, in doing so dispelling a key criticism of psychopharmacology<sup>2</sup>. “People should not lose sight of that fact,” commented Professor Frazer.

He concluded the interview by turning to one of the most recent and striking developments in major depression pharmacotherapy – that of ketamine. “Ketamine has been the most exciting advance in neuropsychopharmacology in the last twenty years, in my opinion. As far as I’m concerned, all the other drugs that have come on the market – including SSRIs and agomelatine – have no advantages compared to the original drugs in terms of efficacy. They don’t make a greater percentage of patients with depression better. They don’t make these patients more better, or better any quicker. They are all equivalent in efficacy, but ketamine may well have improved efficacy.”

But the limitations of esketamine as it stands are several, he explained, including the fact that the nasal spray must be administered under

supervised conditions: “Even though it may or may not be addicting, at least our FDA and drug enforcement agency is not going to let you take home a potentially addicting drug and snort it! That is why it has to be given under these conditions. In addition to raising the cost, though, this is also very inconvenient. It is not the same as taking a pill in the morning in your bathroom. So esketamine may have a limited market.”

“I think what ketamine is going to do is lead us in novel directions for antidepressants that may work through different mechanisms than our original ones and may really have some advantages in terms of efficacy. In the next five or six years, we may be coming up with sons and daughters of ketamine that are even more effective and don’t have its side effects.”

The Meet the Expert session, ‘60 years of antidepressants - where are we now?’ takes place in Attica Hall between 10:30 and 12:00 today.

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## DISCOVERING ADHD IN ADULTS

Meet the experts and immerse yourself in our adult ADHD educational journey

**Saturday, October 5**

**Opening hours: 10:00 –12:00**

**Room: Templars**

Royal Olympic Hotel, Athanasiou Diakou, 28 Athens, Greece

A meet the experts session at CINP 2019. This meeting is initiated and funded by Takeda.

This programme is not intended or eligible for continuing medical education (CME) or continuing education (CE)



*“This will improve my clinical practice”*

Attendee of the ‘Discovering ADHD in Adults’ Session, ECNP 2018

### Faculty



**Larry Klassen, MD, FRCP, BSc** is a psychiatrist and Research chair at the Eden Mental Health Centre in Winkler, Manitoba, Canada. He specialises in the treatment of adults with Mood and Anxiety Disorders, as well as ADHD, and is involved in the ongoing education of psychiatry residents and medical students



**Susan J. Young, BSc (Hons), DClinPsy, PhD, CSci, AFBPS** is the Director of Psychology Services Limited and an Honorary Professor at both Reykjavik University, Iceland and Bucks New University, UK. She is President of the UK ADHD Partnership; Vice-President of the UK Adult ADHD Network; and is a Trustee of the ADHD Foundation, UK



**Josep Antoni Ramos-Quiroga, MD, PhD** is a Professor of Psychiatry at Universitat Autònoma de Barcelona, Spain and is Head of the Department of Psychiatry at Hospital Universitari Vall d’Hebron, Spain

## SYMPOSIUM

Breakthroughs and controversies in mood disorders **Thursday 10:30-12:00**

# Breakthroughs in mood disorders: how can we improve the action of standard antidepressants?

**D**uring this morning's proceedings, a symposium on breakthroughs and controversies in mood disorders explores the latest findings in the mechanisms and genetics of antidepressant response, as well as a look at rapid-acting antidepressants.

The session begins with a presentation by Francesc Artigas (Department of Neurochemistry and Neuropharmacology, Institut d'Investigacions Biomèdiques de Barcelona, Consejo Superior de Investigaciones Científicas (CSIC), Spain; CIBERSAM (Centro de Investigación Biomédica en Red de Salud Mental), Spain; Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Spain), who reviews different mechanisms of action of antidepressant drugs as well as ways to improve the action of standard antidepressants SSRI and SNRI, whose action is mainly based on blocking the reuptake of serotonin.

Over the past several years, Professor Artigas's group have applied molecular strategies based on RNA interference, directed towards genes that limit the activity of serotonergic neurons such as the serotonin transporter (SERT) 5-HT<sub>1A</sub> autoreceptors or TASK-3 potassium channels. In this way, they have evoked antidepressant-like responses in laboratory animals faster and more effective than those obtained with standard drugs.

*"We all have been influenced by Carlos Zarate's findings on ketamine!"*

Francesc Artigas

His group have detailed the principles and strategies currently under investigation to increase the speed and efficacy of antidepressant treatments in a recently published two-paper series<sup>1,2</sup>.

Speaking to *CINP Daily News*, Professor Artigas described some of his recent work.

**In your recent paper on the topic of increasing the speed and efficacy of antidepressant treatments<sup>2</sup>, you outline some very**

**promising results with intranasal administration of SERT-siRNA in mouse. At present, are there any examples of RNAi being applied in clinical practice?**

No, this strategy is still preclinical. In another field – Parkinson's disease – we use the same strategy to reduce alpha-synuclein over-expression. We have some pilot collaborative studies showing it also works in macaque rhesus monkeys, currently unpublished.

We have published a first study in mice, showing that we can deliver antisense oligonucleotides (ASO) selectively to the brainstem monoamine systems (serotonin, dopamine, noradrenaline) in order to reduce alpha-synuclein expression only in these neurotransmitter systems.<sup>4</sup>

**Has the discovery of some of the mechanisms underlying ketamine's rapid action influenced avenues of research exploration in the field of RNA interference?**

Yes indeed. We all have been influenced by Carlos Zarate's findings on ketamine! Some of our recent findings explore the link between glutamatergic and serotonergic transmission.

Changes in glutamatergic neurotransmission in ventral areas of the prefrontal cortex (ventral anterior cingulate cortex in humans, infralimbic cortex in rodents) have a deep impact on serotonergic function.

Our more recent study in this regard includes the development of a mouse model of major depressive disorder based on the siRNA-induced knockdown of astrocyte glutamate transporter<sup>3</sup>, although unfortunately I will not have time to present these data at the CINP Congress.

**How do you envision RNA interference complimenting or exceeding the potential of ketamine as a rapid acting antidepressant? Where is the potential advantage in RNA interference, particularly given the heterogeneity of major depressive disorder pathophysiology?**

Of course, the development of glutamatergic drugs is a really promising avenue in major depressive disorder treatment. The recent FDA approval of ketamine for treatment resistant depression is an excellent example.

However, we know that drugs targeting monoamine systems are very safe and can be taken for decades

without relevant side effects, but we lack information on potential side effects of blocking NMDA receptors for long periods of time since they play critical roles in many brain function, including cognition and memory.

*"RNAi strategies are excellent for the treatment of CNS disorders due to their specificity and selectivity."*

Francesc Artigas

We should not forget that 80% of our cortical, hippocampal or thalamic neurons are glutamatergic.

In this regard, RNAi strategies are extremely selective since they act specifically on given mRNAs, without affecting other protein-encoding RNAs. In my view, RNAi strategies could be used for short periods of time in order to boost the serotonergic system, and once a significant improvement has been achieved, they could be replaced by standard treatments.

**What are some of the outstanding challenges that form the basis of future research directions in this area?**

RNAi strategies are excellent for the treatment of CNS disorders due to their specificity and selectivity. The main limitation is how to deliver siRNAs, ASOs, miRNA, etc. to the brain, and once there, how to target selected neuronal populations. Our strategy of conjugating the oligonucleotides to monoamine transporter blockers is giving excellent results in major depressive disorder and also in Parkinson's disease. It is highly translational, as conjugated oligonucleotides can be administered via the intranasal route. Other groups are using different strategies, but, to my knowledge, none with this selectivity.

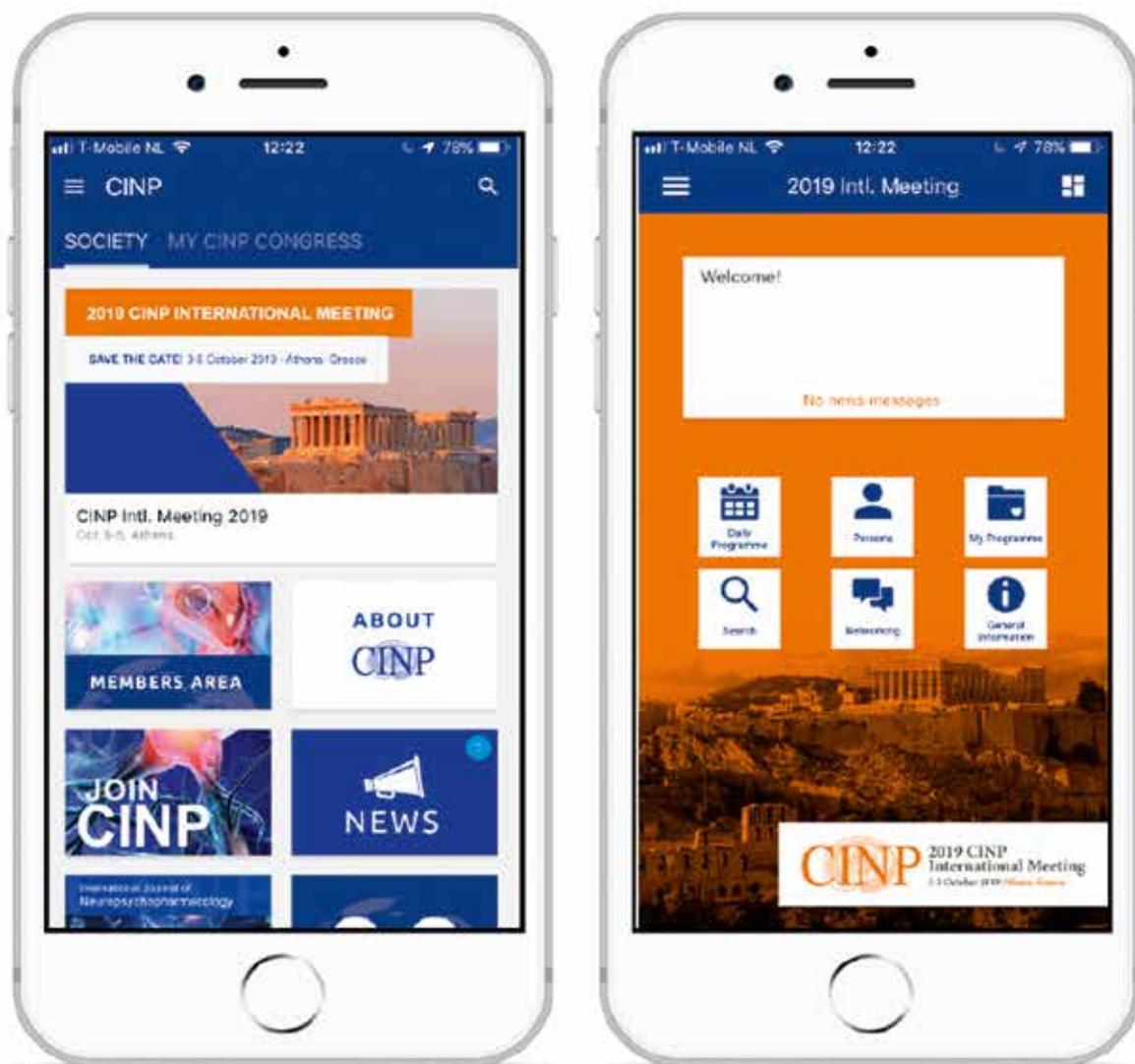
'Breakthroughs and controversies in mood disorders' takes place this morning between 10:30 and 12:00.

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# CINP

## 2019 CINP

### International Meeting

3-5 October 2019 **Athens, Greece**

Symposium **Breakthroughs and controversies in ADHD** Friday 10:30-12:00

## Confounding the pharmacoepidemiological

The effects of the long-term use of attention-deficit hyperactivity disorder (ADHD) medication must be better understood – such is the message of Zheng Chang, assistant professor at the Department of Medical Epidemiology and Biostatistics at Karolinska Institutet (Solna, Sweden) and winner of this year's Rafaelsen Young Investigators Award.

Dr Chang presents tomorrow morning on a recently published qualitative systematic review of pharmacoepidemiological studies into the effects of ADHD medication on behavioral and neuropsychiatric outcomes, of which he is lead author<sup>1</sup>. This is one of the most commonly prescribed medication classes in child and adolescent psychiatry, Dr Chang explained to *CINP Daily News*, with its use also increasing rapidly in adult psychiatry. This formed a central impetus of the study: "There are major concerns remaining about the benefits and risks of ADHD medication, especially in real-world settings."

The review looked at 40 studies from the past 10 years that used linked prescription databases, based in Europe, North America, and Asia. The authors concluded that there are short-term beneficial effects of ADHD medication on several behavioural or neuropsychiatric outcomes (such as injuries, motor vehicle accidents or substance use disorder). They suggested that more replication studies on some outcomes, including criminality, depression, mania and psychosis, are needed.<sup>1</sup>

"There is some good evidence from population-based studies on short-term effects," concluded Dr Chang,

"However, with long-term use there is little high-quality evidence."

Many studies are difficult to interpret reliably, he continued: "When we have a closer look into the studies with regard to the designs and measurements they have used, they are not really good enough to draw a robust conclusion regarding the long-term effects."

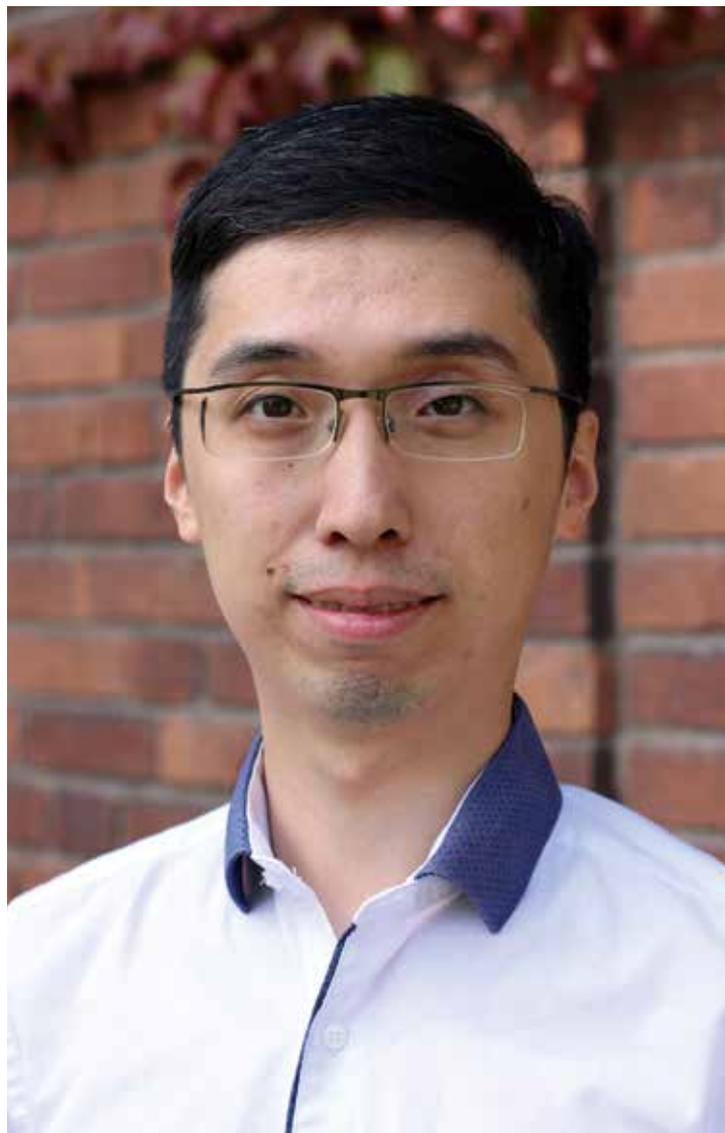
Pharmacoepidemiological studies are markedly different from randomised clinical trials (RCTs), which use randomised treatment assignment and sufficient recruitment of subjects to account for potential confounding factors, whether measured, unmeas-

*"We must think about how we could get better evidence with regards to the long-term effects of ADHD medication."*

Zheng Chang

ured, or unknown. "We have to bear in mind that the pharmacoepidemiology study is an observational study rather than a clinical trial," said Dr Chang. "There are some inherent issues in this, because of the observational nature of the data."

Pharmacoepidemiological studies are prone to bias if confounding is not properly addressed – and indeed, this is not always possible. Such studies must therefore be mindfully designed. "With



confounding, those taking the medication might be different from those not

taking the medication. It is unlikely that they will be randomised, with all

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the background factors balanced between the treated and untreated group. So we must minimise the influence that is introduced by the difference between the treated and the untreated people, such that we can get a causal interpretation of any association that we find.”

Patients with severe ADHD, for example, are more likely to get medication; but because they have more severe symptoms, they are also more likely to have comorbidities such as substance abuse. They are also more likely to have a worse outcome. Another confounder might be that, in the real-world, access to appropriate care can differ according to setting: “Most of the studies that we have conducted have been in Sweden, where there is a universal healthcare system,” noted Dr Chang. “But in other parts of the world, there is more inequality with regards to access to healthcare.” Lack of, or unequal, access to care may have profound consequences on health outcomes, he added, with those affected more likely to experience poor health outcomes.

Such real-world factors are therefore important considerations in carrying out and interpreting studies. Studies must reflect, for example, how exposure to ADHD medication varies over longer periods of time: “People may change their treatment plans, their dosage or even the choice of medication that they receive,” he said. “They may not have perfect adherence either – so they may stop and then restart medication sometime later.”

While clinical trial design has evolved considerably over recent decades, RCTs carry several limita-

*“If we could bring the efforts together, we could provide insights into the mechanisms behind ADHD medications and relieve patients from the functional impairment they suffer from.”*

Zheng Chang

tions – particularly through the lens of patient-centred research and personalised medicine. The need to understand the individual’s disorder trajectory over a possibly expansive lifecourse, rather than the average responses over short time periods typically offered by classic RCT design, suggests the appropriateness of n-of-1 trials. “Because the comparison is within the same individual, all confounding from factors that are stable throughout the observed time at risk is eliminated, even if the factors are unmeasured or unknown,” explained Dr Chang.

He added that only occasionally will an RCT follow-up for as long as two years: “ADHD, in many patients, is a persistent condition so they may have to take medication for many years. We have to consider what that means beyond two, three, five or even ten years in some cases.”

Without sufficiently long-term studies, said Dr Chang, many important outcomes and side effects will be

missed. For example, there is some evidence that some ADHD medications might suppress the heights of children<sup>2</sup>. The possibility of these and other effects ought to be addressed in the long-term, he suggested.

During today’s session, Dr Chang will also describe knowledge gaps in pharmacoepidemiological studies. He highlighted drug interactions as but one example of this: “A lot of ADHD patients are also suffering

*“There could be better designs in pharmacoepidemiology to take care of confounding.”*

Zheng Chang

from comorbidities, such as depression, substance use disorder or anxiety, which also require pharmacological treatment.” As such, many patients are taking multiple drugs, he explained, adding: “So what are

the risks and benefits with regards to polypharmacy? We don’t know if perhaps the drugs interact in some unpredicted way.”

Dr Chang explained that, while his group have found ADHD medication to reduce the risk of traffic accidents, depression and suicidal behaviour, he is increasingly interested in the neurological correlates behind these observations. In this way, the meeting in Athens presents an opportunity as a source of collaboration, he explained: “For me, as a researcher, I can benefit from the CINP society’s knowledge. There is a lot of expertise in the society in a range of fields, from neuroimaging to neuropsychology.

“If we could bring our efforts together, we could provide insights into the mechanisms behind ADHD medications and relieve patients from the functional impairments they suffer.”

Commenting on the significance of winning the Rafaelsen Young Investigators Award, Dr Chang viewed it as an opportunity for developing his research ideas: “It is an important recognition for me as a young researcher in the field. Also, I think it has helped me to better share my knowledge and research work with other researchers in the field. I’m very excited about it,” he said in closing.

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ISSUE 2 OF  
CINP DAILY NEWS  
AVAILABLE FRIDAY

## SYMPOSIUM

Breakthroughs and controversies in psychosis **Olympia Hall** Thursday **13:00-14:30**

## Facing facts in polypharmacy

**G**uidelines on the use of antipsychotic polypharmacy (APP) ought to be revised in light of an emerging review of large representative studies from the past decade. Such is the message of Shih-Ku Lin (Departments of Psychiatry at the School of Medicine, Taipei Medical University, and Taipei City Hospital and Psychiatry Center), who presents the findings of this review during today's session on breakthroughs and controversies in psychosis.

The study, conducted by Professor Lin, rests on the legacy of criticisms of the past regarding the efficacy, side effect profile and costs associated with APP. More recently, prevalence in clinical practice has reflected its broad acceptability, more among certain global regions than others<sup>1</sup>. While opinions have softened in recent literature on the question, criticisms of a lack of quality study have hampered any definitive conclusions<sup>2</sup>.

In his review, Professor Lin considered a number of large-scale studies, which he will explore during his presentation. He also considers patients who require higher antipsychotic doses, as well as deprescribing and the role of adjunctive medication. Broadly, his study finds that a certain proportion of select patients benefit from APP.

Speaking to *CINP Daily News*, Professor Lin described whether current guidelines, which err on the side of monotherapy over APP, reflect the mood within the psychiatry community on the whole as well as prescribing practices. "Most treatment guidelines were generated by consensus meeting of scholars based on evidence-driven publication studies," he began.

"We cannot call this an error, but as we know, clinical studies do not cover every

picture of clinical practices. That is why sometimes physician practices are referred to as a sort of 'art'."

Professor Lin also commented on the premise of arguing in favour of either APP or monotherapy, given the heterogeneity of the patient population. Schizophrenia, he said, is very well known to be both heterogenous in nature, as well as being influenced by individual patients' psychosocial backgrounds. "It is too simplistic to treat a patient by sticking to the guidelines," he summarised.

"I think that treatment guidelines are a kind of reference for prescription. Clinicians have the right to adjust the regimen according to clinical pictures of the patients. But they should not do it based on personal experiences – rather, they should have reasonable reasons."

One of the trials included in the review was that of Tihonon et al (2019), which examines the association of APP versus monotherapy with psychiatric rehospitalisation among adults with schizophrenia. The cohort study included 62, 250 individuals with schizophrenia, with

*"In the revision of new treatment guidelines, the combination of antipsychotics (polypharmacy) should have its own page."*

Shih-Ku Lin

up to 20 years of follow-up. Within-individual analysis was conducted to minimise selection bias, with the finding that APP in general was associated with slightly lower risk of psychiatric rehospitalisation than monotherapy. The investigators found that certain drug combinations (e.g. clozapine plus aripiprazole) were associated with reduced rehospitalisation



compared with others.<sup>3</sup>

Asked whether he considered that there is sufficient evidence of this nature at present regarding the most effective drug combinations for specific patient subsets, Professor Lin replied: "From the results from this big number dataset with 20 years' duration of follow-up, it indeed shows that certain type of antipsychotic combinations can have a better outcome than monotherapy."

Care must be taken, however, when interpreting studies such as this. "What we should be cautious of is that clozapine dominates the results, and this study was carried by within-individual design. Considering the side effects of clozapine, it should not be used as the second line ones. If this kind of combination (clozapine and other antipsychotic) is proposed, then I would suggest a low dose of clozapine (around 300 mg for Caucasians and 150 mg for Asians)."

Professor Lin urged that guideline revision take place regarding how polypharmacy

is conducted, noting: "The trend of polypharmacy is inevitable in psychiatric prescription nowadays. This is not only the case in the treatment of schizophrenia, but also in bipolar disorder, major depression and many others.

"We need to face this fact. In the revision of new treatment guidelines, the combination of antipsychotics (polypharmacy) should have its own page. Stahl (2013)<sup>4</sup> has proposed a dozen suggestions that we can apply at the moment."

He also discussed deprescribing as another important issue in this area. Clinicians should from time to time review the medications according to the clinical picture presented by each individual patient, he advised, rather than maintaining the same medications unquestioningly. "The golden rule is that we should keep the simplest medications and lowest dose during maintenance treatment phase."

Concluding with his opinions on study design in clinical studies of real world prescribing practices, Professor Lin considered the commonly adopted endpoints of mortality and rehospi-

talisation, which represent useful but surrogate markers of patient quality of life. Considering how more direct reporting of quality of life for patients with schizophrenia could be achieved, he commented: "This is a very interesting issue.

"These two indicators [mortality and rehospitalisation] are much easier to be analyzed in big datasets, so lots of studies select them as primary outcome. These results only reflect the official or authoritative point of view, rather than the feelings of the patient themselves.

"In my own study (Chen and Lin, 2016)<sup>5</sup>, I applied the World Health Organization's Quality of Life and Subjective Well-being under Neuroleptic Scale questionnaires to evaluate patients under long-acting antipsychotic (LAI) treatment. Contrary to our original hypotheses, it was interesting to find that patients under first generation LAI had a slightly better outcome than second generation LAI – the determining factor was that first generation LAI group had a much longer duration of LAI treatment."

Professor Lin speaks during the symposium, 'Breakthroughs and controversies in psychosis', taking place in Olympia Hall at 13:00-14:30 today.

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## YOUNG SCIENTIST FORUM

How to get your career on track early **Templar's Hall** Thursday 10:30-12:00

# Getting your career on track early

This morning sees a wealth of experience on offer for budding scientists and psychiatrists, in a Young Scientist Forum led by Joseph Zohar and John Krystal.

Professor Zohar, who is the director of Psychiatry and the Anxiety and Obsessive Compulsive Clinic at the Sheba Medical Center in Tel HaShomer and professor of psychiatry at Tel Aviv University, Israel, told *CINP Daily News* who should be attending the session, and what they can learn.

*“If you would really like to do it, you need to dare and start it.”*

Joseph Zohar

**At student level, it is sometimes the case that it is not taught how to be a scientist who is active in directing their career, in terms of getting grants, formulating good research questions, networking, etc. How will the session be tackling this?**

I think that for many psychiatrists or scientists at this level, it is not clear for them how to do it. They would like to do it, some of them. But it seems to them that it is complicated. Many times, they don't have a mentor to help and guide them.

The idea of the session would be to give them a perspective about this, and to do this through personal stories and experiences, to give them a better picture of how one can go about this.

There is also going to be a bit of space for Q&A. The idea is that, by the end of the session, those who would like to pursue this kind of avenue will have a better idea and a clearer picture of how to start.

**In general, what efforts does CINP make to involve young scientists?**

There are specific efforts to attract young scientists. This and other workshops are a part of this effort. All the time when we are doing any scientific programme for CINP, or planning any seminars or meetings, we dedicate specific attention to creating a specific space for young scientists and young psychiatrists – a place in which they can communicate amongst themselves and a place where they can interact on a personal level with senior faculty.

**What resources are there outside of the conference setting that you would recommend in terms of learning about opportunities and pitfalls?**

There are a lot of other resources. In the scientific meeting, and this particular session, the idea and the target is to open the doors and open the eyes of young scientists and young doctors, for them to learn about where they should go.

But there are also a lot of grant opportunities, a lot of exchange programmes, a lot of educational programmes, and so on. I think many of them are not fully aware of these.



*“We dedicate specific attention to creating a specific space for young scientists and young psychiatrists.”*

Joseph Zohar

In this meeting, we will learn about what they should do when they come back from the meeting, what kind of possibilities are out there, what they should do in order to start the process.

You are distinguishing the young psychiatrist who may be interested in conducting research from the neuroscientist, whose central role it is to do this.

The real way to distinguish is by looking at clinical versus preclinical research – or preclinical and clinical research versus only preclinical research. For each of these four groups, the pure clinical, the preclinical and clinical, the only preclinical, and the combination of all of these, there are different grants and the way that you should approach each of them is different.

This is why the participant should first define for themselves where they would like to be. Then, after making that decision, there are different ways that one could approach getting to the end of that road.

**Are there any aspects of learning that you see growing in importance in the near future?**

Digitalisation and information technology are changing the landscape of research, especially clinical research. This is something that people need to be aware of and think about, and try to incorporate in their future research – not just digitalisation, but also digital health.

They will need to think about out-of-the-box, new ways to conduct and analyse studies.

**What is the central message you would like to convey to those starting out?**

From the outside, to somebody who is about to start out it all can look somewhat frightening. One of the ideas in this symposium is that, if you would really like to do it, you need to dare and start it. Then you will find that it is not as difficult or frightening as it seems in the beginning.

The Young Scientist Forum 'How to get your career on track early' takes place between 10:30 and 12:00 today in Templar's Hall.

## KEYNOTE LECTURE

The future of manualized versus personalized psychiatry **Olympia Hall Thursday 14:30 - 15:30**

# The future of manualised versus personalised psychiatry

In a keynote lecture this afternoon, Tarek Okasha (Ain Shams University, Cairo, Egypt) tackles the current era of manualised psychiatry, defining the reasons for moving towards personalised psychiatry, which constitutes treatments provided on pharmacological, aetiological, symptomatic and prognostic bases.

Professor Okasha is Director of the World Psychiatric Association (WPA) Collaborating Centre in Research and Training in Psychiatry, and is a member or honorary member of many international associations and organisations.

He is also Editor-in-chief of the *Middle East Current Psychiatry Journal*, and Associate Editor of the *Egyptian Journal of Psychiatry*. He co-authored the recently published Lancet Psychiatry paper on mental health research in the Arab region, a roadmap for Arab mental health researchers and research institutions, which seeks to address the gap in research productivity in the Arab region relative to and the rest of the world<sup>1</sup>.

Professor Okasha spoke to *CINP Daily News* to discuss the theme of his keynote lecture today. He began

by defining what is meant by personalised psychiatry, as well as the needs of both the clinical and research spheres in this vein.

"Psychiatry, as a branch of medicine, is one of the very few branches that is not based on aetiological diagnosis," he said.

"This means that it is a cluster of symptomatology with which we start to diagnose the disorder itself. However, we do not have a diagnosis based on laboratory findings, MRI, PET scans, or whatever else.

"The whole idea is that psychiatry is moving, and should be moving, towards having something different, which is the aetiological diagnosis. The problem is that at the moment we really need manualised psychiatry in order for it to help us with several things. First of all, we need it in order for us to have a common

language to speak with. We should have it in order to be able to have research between different countries and different organisations."

The current need for manualised psychiatry is not a denial of its shortcomings, however. And these are several, noted Professor Okasha. For example, he said, they are not culturally sensitive enough. In addition, they do not take into account the high rates of comorbidities that are evident in psychiatric disorders: "We have in some cases levels of comorbidity that reach up to 50-70%. That means that there is something wrong with our manuals."

He continued: "There are also difficulties that are related to research methodology. At the same time, we have to keep in mind that sometimes medications might change the diagnosis, whenever a new drug comes out that we are able to use in a certain diagnosis."

Moving on to discuss personalised psychiatry, which he defined as psychiatric treatment individualised according to each patient, Professor Okasha cite five main components. First, he said, personalised psychiatry must be specific to the individual in

question. Second, it must be participatory, such that the patient and the doctor understand each other and reach a consensus on management strategies. Third, it must be predictive, in terms of the risks associated with a given medication in a particular patient, as well as the chance of its success in ameliorating certain symptoms, the appropriate treatment length, when it should be discontinued, and so on.

The fourth component of personalised medicine is that it needs to be preventative, he said, elaborating: "Instead of treating disorders when the symptoms appear, we should have a form of treatment which can either prevent relapses that could occur – or, if you want to dream a little bit more, to prevent the occurrence of the disorder itself. That is a big dream.

"Last, but not least, it should be psychocognitive, meaning that we also have to bring the cognitive functions of the patient and the psychological aspects of the patient into consideration."

While this has already begun, he added, the field is still taking its first steps. "We have some things that are promising. For example, we

now have the connectome – a method with which scientists are trying to see the connections within the brain of nerve tracts for depression, for obsessive compulsive disorder, for schizophrenia, and so on. With this, we are not just trying to diagnose symptomatology, or defining which neurotransmitters are affected, but we are looking for structural changes in the brain that can be measured.

Then, after treatment, we can see improvements. This is something that we might see in the next ten or 15 years.

"We also have pharmacogenomics, where according to the genome of the individual we might be able to predict which medicine they are going to respond to. This is not a

*"We are not only moving away from manualised psychiatry, but also moving towards pharmacogenomics, the connectome, nanopsychiatry."*

Tarek Okasha

dream: it is already occurring in the treatment of some disorders, especially in cancer treatment. We hope that it will happen in psychiatry as well. And, by the year 2050, there are people talking even now about the concept of nanopsychiatry – the use of nanomedicine to work with patients with psychiatric diagnoses."

"So it is very interesting that we are not only moving away from manualised psychiatry, but also moving towards pharmacogenomics, the connectome, nanopsychiatry," he concluded.

The shift away from categorical diagnostic manuals is an acknowledgement of the unique needs of individual patients, he said. Contrasting the concept of personalised medicine with the biopsychosocial approach, he explained: "The biopsychosocial model is very interesting, but it is too vague. When we say 'psychological', 'social' and 'biological' factors – this encompassing everything in the world affecting the patient. If we are able to personalise psychiatry for every person, that would be wonderful. If we can personalise it in a manualised way in order to help research, that would be even better."

*"Psychiatry is moving, and should be moving, towards the aetiological diagnosis."*

Tarek Okasha



Professor Okasha speaks today at 14:30-15:30 in Olympia Hall.

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## SYMPOSIUM

Breakthroughs and controversies in mood disorders **Olympia Hall Thursday 10:30-12:00**

# Embracing complexity in cutting edge pharmacogenetic research

**D**uring this morning's session on breakthroughs and controversies in mood disorders, Alessandro Serretti (Department of Biomedical and NeuroMotor Sciences, University of Bologna, Italy) speaks on the genetics of antidepressant response, highlighting the significance of recent advances in pharmacogenetics that are set to bring about the long anticipated successes in guiding clinical decision-making and research.

The main findings of antidepressant pharmacogenetics of the past twenty years are described in a recent review co-authored by Professor Serretti<sup>1</sup>. Speaking to *CINP Daily News* ahead of the session, he explained that pharmacogenetics seeks to predict treatment response as well as inform the development of novel treatments: "This is the final aim, but we are not there yet."

"There are some things that are already well known, related to the pharmacokinetic genes – the cytochrome genes, which control enzymes in the liver that metabolise the drugs and hence controls their plasma levels<sup>2</sup>. This is already well known and it is on the label of many of our compounds."

"This is the easy part. The more complex part is the drugs that control for proteins in the brain. Here, we are still working on it of course."

Candidate gene studies, such as those that looking for single nucleotide polymorphisms (SNPs) of the serotonin transporter or brain enzymes have not yielded solid results. Indeed, said Professor Serretti, the method of investigating lone candidate genes has fallen out of favour, largely because of the acceptance of the polygenic nature of psychiatric disorders including depression, as well as the advent of more recent techniques such as genome-wide association study (GWAS) and the more recent multi-marker approaches.

"The strategy now is to find a combination of genes across the whole genome, which is quite successful in other areas of medicine, such as cardiology," said Professor Serretti. "This is the so-called polygenic risk score (PRS), which includes hundreds of genes."

The concept underpinning more sophisticated approaches such as gene and pathway analysis or PRS is that SNPs act in an interrelating fashion, both within and between genes. In



psychiatric disorder, this contributes to observed neurobiological and behavioural phenotypes.

Recent dissatisfaction with GWAS is rooted in the fact that, unlike multi-marker approaches, it cannot adequately model the polygenic nature of response to psychiatric drugs. "GWAS that we have now are mainly focussed on the most significant findings," said

*"The multi-marker approach, in my opinion, will be the future."*

Alessandro Serretti

Professor Serretti. "But there is not one or two or five most significant findings – there are hundreds of small modulators. This is why a shift in the methodology of analysis is needed."

This feature of GWAS means that, in practice, relevant polymorphisms may not reach significance thresholds, because they are pitted against a background of hundreds or thousands of other candidates. Professor Serretti also cited the limitation of the preselection of only common variants in GWAS, meaning that pertinent but

rarer polymorphisms contributing to antidepressant response are overlooked. "This is a very relevant issue," he commented. "This is why all the groups worldwide are now focussing on exome sequencing and whole-genome sequencing."

As described in his recent review paper, PRS is an approach to estimate an individual's tendency to a particular phenotype. It represents the cumulative effect of a number of variants upon a complex trait. And while the authors point out that no reliable predictor of antidepressant response has emerged from PRS approaches, further refinements – such as the study of more homogenous patient groups, or of the additive effects of PRS and stressful life events – may bear better fruit. "I believe in this approach," said Professor Serretti, "Because the reality is that the modulation of the effect of drugs is due to hundreds of different elements that interact together."

"You respond better because of the serotonin system, the glutamate system, the GABA system, etc. – a large-scale interaction. In fact, the most recent studies into PRS define a possible profile risk. The next stage is to go even deeper, not only including PRS from GWAS (which are not so precise), but exome sequencing and whole-genome sequencing. This

way, you have a complete coverage of the genome."

Contrasting the multi-marker concept with the emerging market in commercial genetic testing, he continued: "The multi-marker approach, in my opinion, will be the future<sup>3</sup>. But there are already many companies (about 40-50) worldwide that are selling to doctors, and sometimes to patients, the prediction of antidepressant response. This is based on a small number of genes – maybe five or eight."

"My opinion, and the opinion of many, is that these results are not very useful in clinical terms, because we are just not stable yet. The serotonin transporter gene, for example, is not that relevant in all subjects. The only answer must come not from five or eight genes, but from hundreds of genes in a combinations that we do not know exactly at present."

Accompanying this are the advanced statistical models and algorithms of machine learning, which is being explored to make sense of the emerging multi-gene and non-linear data: "With the non-linear models that we are using at present, we are able to make predictions that are much more reliable. The relative contribution of each gene and protein is combined in the best way (this is not something we can know in advance, or course), and it must be combined with clinical aspects too – clinical predictors are very important in antidepressant response. So you should combine hundreds of SNPs with 10-20 clinical variables and, in combination with machine learning, you have a clinically useful prediction."

Asked whether efforts are being made to improve the ethnic and geographical inclusiveness of the data landscape of ongoing genetic studies, Professor Serretti responded that such important issues persist in many fields of research, not just in pharmacogenetics and psychiatry. "The problem is that many samples are actually from Caucasians. We have much less information about Asians, and even less about African ethnicities. A big effort should be aimed at collecting samples from these areas, because the predictions obtained in Caucasians is not completely applicable to other ethnicities. There are shifts in the sequence of SNPs and the frequency of SNPs."

He also addressed whether the

goals of pharmacogenetic tool development have shifted, drawing away from preemptive applications (i.e. prior to prescribing) towards those patients who have failed at least one previous treatment: “Yes, and no,” he replied. “When you have a patient that already has not responded, you already know part of the story. So it is somehow less useful to know what is the genetic background of this patient.

“It is much more important to know in advance before the first treatment. This is the phase where you maximise your clinical impact and cost-benefit (economically, as well as on a subjective well-being level). The

genetic profile can be useful, first to know if a patient will be resistant. And ideally, even though it is not available yet, it is useful to know which compound the patient will respond to best. This is exactly what I hope will happen in a few years from now – that we can have a very easy genetic analysis available for all clinicians that give them the risk of resistance of the patient, and an indication for the choice of compound.”

He further underscored that present methods that are on the market have not yet been completely tested, and appear to lack the necessary complexity to represent a truly useful clinical tool. “There is a message of

caution here,” he said. “These companies are marketing their products, but we still don’t have so much evidence that they are useful. Sometimes they could also be harmful. If a clinician follows a suggestion, but the suggestion does not apply to that patient, he or she is making a mistake.

“I will present one interesting case where, because of genetic testing, the patient was not treated with the drug that eventually turned out to be most useful for him. Some clinicians might be following genetic testing, but it is probabilistic and still not very strong evidence. As such, mistakes can be made. This is my message to clinicians.”

The session ‘Breakthroughs and controversies in mood disorders’ takes place this morning at 10:30–12:00 in Olympia Hall.

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