CINP

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CINP DAILY NEWS

THE OFFICIAL NEWSPAPER OF THE 2019 CINP INTERNATIONAL MEETING

"Psychopharmacology is a holistic discipline"

Delegates were welcomed to the CINP International Meeting yesterday morning by its President Siegfried Kasper alongside a number of local guests, whose words encapsulated the significance of the meeting's setting in the cradle of occidental culture, as well as the significance of the scientific programme itself.

"I have to say I think we have the top neuropsychopharmacologists worldwide together in this programme," commented Professor Kasper, before introducing Local Organising Committee Chair Kostas Fountoulakis. Professor Fountoulakis addressed the symbolism that the city of Athens holds over psychiatry and the scientific world more broadly. "The CINP is, chronologically, the first real scientific community in the field of psychiatry.

"This congress takes place exactly on the site where science was developed for the first time on the two coasts of the Aegean, in Athens and the city of Miletus. Some 2,500 years ago there was the first man who said, 'We need to go beyond the metaphysics and see nature with the eyes of a scientist.' This was Thales of Miletus.

"Psychopharmacology should be and is a global discipline."

George Christodoulou

"This was the first time mental disorders were considered as natural phenomena. Then, there was the school of Hippocrates. Just before that, it was Pythagoras that said that the brain, not the heart, is the seat of the mind. So it is of great symbolic value and importance that we have the CINP here today."

Constantin Soldatos, Honorary President of the World Federation of Societies of Biological Psychiatry (WFSBP), commented: "The two organisations, CINP and WFSBP, are broadly related because we have had the same presidents over the years. But we also have common interests.

"The programme here is rich and challenging. I would single out one presentation by Hans-Jurgen Moller – 'Evidence does not equal evidence'. I am anxious to listen to his talk and all the talks of eminent speakers."

Concluding the proceedings was George Christodoulou, Honorary President of the Hellenic Psychiatric Association and President of the Society of Preventive Psychiatry, who stressed the importance of CINP in promoting psychopharmacology. "As you know the current trend is of personified psychopharmacology, in the sense that everybody needs – on the basis of biological parameters – special management and treatment.

"This coincides with the personalised psychiatry movement, which runs not in the same, biological, direction, but rather in a psychological and sociological direction. But every psychological phenomenon of course has biological parameters. So there is a convergence of the two movements. We have crosstalk, and I am very glad that these two directions are following the same path: person-centred psychopharmacology and person-centred psychiatry."

He added his elation at the substantial Greek participation in the meeting, as well as highlighting the symposium of the Hellenic Psychiatric Association. In his capacity as Honorary President of the Psychiatry Association of Eastern Europe and the Balkans, he also spoke of the significance of participation from other Balkan areas: "I stress the importance of promoting psychopharmacology in these countries in the Balkans, which have been deprived of scientific knowledge during the last decades. It is important to cooperate with

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Welcome **Olympia Hall** Wednesday **8:30–9:00**

"Psychopharmacology is a holistic discipline"

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the Balkans and especially with the Psychiatry Association of Eastern Europe and the Balkans."

Professor Christodoulou's final point derived from his efforts to promote psychiatry and mental health in Athens and the rest of Greece: "I have noted that psychopharmacology is associated with pill-taking," he said. "It is degraded. People – especially those without any qualifications, but even many psychologists – tend to state that psychiatrists are people who give pills. This reduces psychopharmacology to something that is not desired."

He said in closing: "Psychopharmacology should be and is a global discipline, taking into account the psychological, the biological, the social parameters. It is a holistic discipline. We should move towards this direction to face all these problems which are promoted by people who are against psychopharmacology, who are trying to reduce the discipline to just pill-taking."

CINP Daily News

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Programme: Friday 4 October

08:30			
09:00	**09:00 – 10:00** **Oldrich Vinar Keynote Lecture** **Treatment resistant depression** *Siegfried Kasper*		
09:30			
10:00	**10:00 – 10:30 Coffee Break**		
10:30	**10:30 – 12:00** **Symposium** **Breakthroughs and controversies in ADHD** *Zheng Chang, Larry Klassen, Andrea Cipriani*	**10:30 – 12:00** **Meet the Expert** *Konstantinos Fountoulakis*	**10:30 – 12:00** **Workshop** *Joseph Zohar, Pierre Blier, Hans-Jürgen Möller*
11:00			
11:30			
12:00			
12:30	**12:00 – 13:30** **Lunch / Poster Viewing**		
13:00			
13:30			
14:00	**13:30 – 14:30** **Keynote Lecture Antidepressants work: the evidence** *Elias Eriksson*		
14:30			
15:00	**14:30 – 16:00** **Symposium** **Breakthroughs and controversies in insomnia** *Andrew Krystal, Pierre Michel Llorca, Gabriella Gobbi*	**14:30 – 16:00** **Meet the Expert** *Larry Klassen*	**14:30 – 16:00** **Workshop For Young Clinicians** *Pierre Blier*
15:30			
16:00			
16:30	**16:00 – 16:30 Coffee Break / Showcase Presentation by Janssen**		
17:00	**16:30 – 17:30** **Keynote Lecture** **Neuroactive steroids as rapid-acting antidepressants: the story of brexanolone and SAGE-217** *Stephen Kanes*		
17:30			
18:00	**17:30 – 18:00 Guided Poster Session**		

SYMPOSIUM

Breakthroughs and controversies in insomnia **Olympia Hall** Friday **14:30–16:00**

Living the dream: Drug discovery in insomnia

Gabriella Gobbi, professor at the Neurobiological Psychiatry Unit at McGill University (Montreal, Quebec) chairs this afternoon's symposium on breakthroughs and controversies in insomnia. She will also be delivering a presentation on the drug discovery process relating to a promising candidate of sleep promotion that may reduce risks of addiction or motor impairments.

In an interview with *CINP Daily News*, Professor Gobbi explained that this research began a decade ago, during her studies of the G-protein coupled melatonin MT1 and MT2 receptors and their roles in the sleep.

"I ended up in the field a little bit by serendipity," she said. "This was part of a collaboration with a group of chemists from Italy; we started to test some specific selective compounds that act on the MT1 and MT2 receptors in our lab."

Professor Gobbi and colleagues conducted preclinical studies using melatonin receptor agonists: "We looked at their effects on behavior such as anxiety, depression and sleep and we saw that these compounds were very effective on sleep," she added.

They also looked at selective agonists of the MT2 receptor, finding it to decrease the latency to the first episode of non-rapid eye movement (NREM) sleep, as well as increasing the total amount of NREM sleep, while having no influence upon REM sleep.[1]

Comparisons were then made of the selective MT2 agonist against relative to MT1/MT2 non-selective agonists, which include melatonin, with the finding that these did not produce significant effects on sleep stages. This seemed to indicate that the MT2 receptor subtype was the principal one involved in the regulation of NREM sleep, while the MT1 may in some way act as a counterbalance promoting awakedness (although a paucity of selective MT1 receptor ligands has limited the validation of this notion).[1]

Currently, a number of non-selective agonists of MT1/MT2 receptors, aside from melatonin, are approved by different drug agencies. Because their mechanisms of action do not affect the opioid receptors, they are perhaps viewed as a less risky alternative to benzodiazepines in sleep disorders. The issue remains, however, that non-selective agonists of MT1/MT2 receptors are not always effective. "We noticed that melatonin has a kind of soporific effect, and a weak effect on sleep," said Professor Gobbi.

With this in mind, she and colleagues have generated data to validate a selective MT2 agonist that selectively enhances NREM sleep, UCM924, by pharmacological and genetic approaches, as detailed in Gobbi et al (2019)[1]. "We could see that if you bind only the MT2 receptor, you can have a strong effect on sleep," she said. "It's been a long process. This is the process of drug discovery starting with a chemical structure, and a lot of tests in animals."

This afternoon, Professor Gobbi will present the story of this drug discovery process, including the original structural chemistry, ligand binding studies, studies of MT1, MT2 and double knockout mice, and immunohistochemistry studies of receptor expressions in the brain. Data so derived support the assertion that MT1 receptors are mainly implicated in the regulation of REM sleep, whereas the MT2 receptors selectively increase NREM sleep.

"There are so many undiscovered receptors in our brain that could result in new molecules, and new drugs for mental health."

Gabriella Gobbi

Professor Gobbi's team have also discovered other potential uses of UCM924: "We discovered that not only is UCM924 good in sleep, but that in low doses it is also good for chronic pain.

"Because today the problem of pain is to do with the opioids scandal, it is very important to find an alternative to these – just as it's important to find an alternative to benzodiazepines."

UCM924 is now being taken towards phase I trials: "We are working to have a bioavailable drug and investigational new drug (IND) approval to start clinical trials," she said, adding that she intends to explain the IND process during her talk – largely because it is uncommon for university research to reach this level in the drug development process. "We are quite unusual. It is very difficult to develop a drug to the IND stage. We are at the academic level and it's risky; staff and other resources are limited. But at the same time, I have had a chance to work with high-class chemists and people in drug discovery."

She went on to recall that, in the early years of her research into the melatonin receptors, she encountered scepticism. Today, the field remains small: "There are very few researchers investigating the function of these receptors. It would be nice to have more research and more industry involved in this field."

Professor Gobbi concluded with some words of encouragement for the field of drug discovery in mental health in general: "We don't have many new targets, new medicines and we don't have any new paradigms," she explained. "It's very important to discover new targets and new receptors that can address the problem of insomnia and pain, because today one of the main issues of health is to find an alternative to opioids and benzodiazepines."

"We saw that these compounds were very effective on sleep."

Gabriella Gobbi

"It's important to expand our horizons. There are so many undiscovered receptors in our brain that could result in new molecules, and new drugs for mental health. The message is if we really want novel drugs for mental health, we have to invest in more innovative research and look at the receptors that are underexplored," she said in closing.

The symposium 'Breakthroughs and controversies in insomnia, takes place in Olympia Hall today at 14:30–16:00.

Reference

1. Gobbi G, Comai S. Differential Function of Melatonin MT1 and MT2 Receptors in REM and NREM Sleep. Front Endocrinol (Lausanne). 2019 Mar 1;10:87.

SYMPOSIUM

Breakthroughs and controversies in insomnia **Olympia Hall** Friday **14:30-16:00**

Benzodiazepines: how to balance their benefits and risks

Pierre Michel Llorca, a specialist in schizophrenia and mood disorders at CHU Clermont-Ferrand, France, continues this afternoon's session on breakthroughs and controversies in insomnia with a presentation on treatment strategies using benzodiazepines.

"I work with the consequences of sleep disorders, including insomnia, in patients suffering from schizophrenia and bipolar disorder," Professor Llorca told *CINP Daily News*.

As an expert in both pharmacological and psychotherapeutic treatment of sleep disorders, during his talk Professor Llorca will look at the benefits and risks of benzodiazepines in the treatment of insomnia, focusing on his own data derived from a cohort of patients with bipolar and schizophrenia that he has been researching for some time.

Benzodiazepines have been in clinical use since the 1960s, in 1977 reaching the dubious position of most-prescribed medication globally. As a treatment option, cautioned Professor Llorca, they remain a double-edged sword: "For more than 40 years, benzodiazepines have largely been used to treat sleep disorders and insomnia in the general population as well as in the psychiatric population. They are widely used because they are very efficacious, but also because there are few real alternative and convincing solutions out there.

"Benzodiazepines have been so easy to use that they've been prescribed not only by psychiatrists, but also by general practitioners and many other specialties for years."

The dangers of benzodiazepines are well documented. "It became a public health problem because unfortunately it can result in dependency. In France, it's largely been used without prescription by patients, who always seem to have an old box of sleeping pills in the cupboard."

Professor Llorca added that the addiction risk extends even to non-benzodiazepine drugs, such as the more recently introduced zolpidem: "In the department I'm running, we have a lot of cases of real abuse of zolpidem. This is a really big problem and difficult to treat. These drugs have become quite a public health problem, and we have a lot of recommendations and restrictions in many countries."

"Benzodiazepines are a very useful tool and very powerful, on the other hand the risk means it has to be used very cautiously to avoid problems."

Pierre Michel Llorca

As well as addiction risk, sleeping pills are also associated with day-to-day hazards, such as falls – particularly in the elderly population.

Despite such issues, however, benzodiazepines remain undeniably efficacious in treating sleep disorders, he stressed. "Another advantage of benzodiazepines is that they have an effect in sleep disorders in some of the most vulnerable patients."

Particularly significant is the relationship between sleep disturbance and the onset of psychiatric symptoms: "We have observed that very frequently – and different studies confirm this – that the modification of sleep rhythm and sleep disorder can be very early signs of relapse in schizophrenia patients. It can increase vulnerability and trigger a relapse."

Professor Llorca will present data supporting these assertions. "These data are important because they could [be applied to] reduce vulnerability to relapse," he explained.

Therapy to tackle sleep disorders in the psychiatric population, particularly those individuals with bipolar disorder and schizophrenia, includes both medical therapy and psychotherapy. Professor Llorca cautioned that care must be taken not only in terms of handling the risks of medical treatment, but also in ensuring that treatment is appropriately timed. Choice of medication is also important, with some only demonstrating a limited impact on sleep (e.g. melatonin), while others carry unignorable side-effects (e.g. zolpidem).

While Professor Llorca's department have developed psychoeducational strategies, including those for community use, success in this vein has been limited: "These [strategies] are not so easy to develop, and the efficacy is really difficult to compare to sleeping pills."

For these reasons, despite their issues benzodiazepines represent a promising strategy. "The question is, how do we balance between their pros and cons?

"Benzodiazepines are a very useful tool and very powerful, but on the other hand their risks mean that they must be used very cautiously to avoid problems."

Professor Llorca proposed a management strategy centred upon in-depth understanding of the individual patient, with careful consideration of risks associated with benzodiazepine use, including addiction, confusion, interactions with other drugs, and suicide.

He advised: "We must have a precise evaluation of the sleep disorder. It is important to relate this to the specific history of the patient. It is very common to have sleep disorders in the clinical population, but they can vary from one patient to another. The specificity of the sleep disorder is important.

"My recommendation would be that they must be used under very specific conditions, by specialists, with a very good evaluation and a plan of prescription that is very precise and that has been explained to the patient. It has to be decided using the tools of shared decision-making."

Professor Llorca's data on the pros and cons of benzodiazepines come from a national project, of which he is principal investigator. This scientific collaboration, Fondation FondaMental[1], was initiated in 2007 and consists in a network of expert centres for bipolar disorder, schizophrenia, treatment resistant depression and autism. Its aim is to improve the diagnosis, assessment, and management of psychiatric pathologies. Professor Llorca is on the steering committee of the foundation.

"We are running cohorts of bipolar, schizophrenia patients, treatment resistant patients, as well as Asperger's patients," he explained.

The project focuses on national and regional centric cohorts: "We are validating patients every year over five years, trying to evaluate the impact of treatments in different ways. We work on a lot of clinical evaluations and have results surrounding the modification of sleep and sleep disorders in the clinical population and the relationship with the risk of relapse."

"These data are important because they can reduce vulnerability to relapse."

Pierre Michel Llorca

Commenting on today's session, he concluded: "I am very interested in being part of this conversation, because there will be data on different compounds in development. So perhaps we will have more options in the future.

"When we look at the recent past, we've only really had benzodiazepines or non-benzodiazepines to choose from. The pros and cons of these are largely similar.

"That's one reason to keep in mind that, when we are discussing the patient and whether or not to prescribe, we must decide on a case-by-case basis, what is the balance between the benefits and risks."

The session 'Breakthroughs and controversies in insomnia' takes place today at 14:30 in Olympia Hall.

Reference

1. Fondation Fondamental website. www.fondation-fondamental.org

SYMPOSIUM

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

Network analysis addresses knowledge gaps in clinical decision making

Network meta-analysis, a statistical technique that enables head-to-head comparisons of multiple interventions, will be discussed today by Andrea Cipriani (Professor of Psychiatry at the University of Oxford, UK) during a session on breakthroughs and controversies in attention deficit hyperactivity disorder (ADHD). His team recently applied systematic review and network meta-analysis in comparing the efficacy and tolerability of seven ADHD therapies against each other and placebo[1].

Professor Cipriani spoke to *CINP Daily News* ahead of the session. "I will talk about our study in terms of analysis and interpretation," he said. "But my main contribution is the methodology, because for the first time in the field we have managed to summarise all the published and unpublished data about pharmacological treatments for ADHD in children, adolescents and adults."

He and his team have also recently applied network meta-analysis in a similar way in schizophrenia[2] as well as in major depression[3].

The strength of network meta-analysis in the context of drug trials is that it allows comparisons among multiple treatments that have not been – and perhaps will never be, due to its practical infeasibility – directly compared. Standard meta-analysis involves the assessment of evidences pertaining to one treatment versus another at a time, pooling together trial data that compare these specific two treatments and that fall within patient- and methodology-related inclusion criteria. Hence, some head to head efficacy can be estimated. But, noted Professor Cipriani, this standard method falls short when it comes to facilitating comparisons between the multitude of available drugs for a specific condition, complicated further by the fact that some head-to-head comparisons may be absent entirely. "What happens when you have a trial testing A versus B and another testing B versus C, but there aren't any trials of A versus C?" he posed, adding: "If you want to compare treatments A and C and you don't use the [network analysis] methodology, the answer is [nothing, because] there are no data available."

He continued: "We can compare A versus C using the indirect evidence from A versus B and B versus C. We basically build a network of treatment and combine all data directly and indirectly to compare each pair of interventions. In the end, you can present the results from all possible comparisons of treatments."

Network meta-analysis has gained ground as a tool in developing clinical guidelines, produced by agencies such as the National Institute for Clinical Excellence. Professor Cipriani has collaborated on such recent guidelines for bipolar disorder and depression. "They give clinicians, policymakers and patients an overall picture of the evidence, even if you don't have the specific trials comparing treatments."

"This is the first time that a fully developed method like network meta-analysis has been used for ADHD pharmacological treatment in children, adolescents and adults."

Andrea Cipriani

Clearly, there are limitations to any analytical method that involves indirect comparison of datasets A and C by way of their common comparator B, and Professor Cipriani will highlight these during his talk. "There are some assumptions that are crucial in order to understand whether these indirect comparisons make sense," he stressed.

These assumptions include: similarity or exchangeability, controlled by inclusion and exclusion criteria; homogeneity between different trial results under comparison; and transitivity and consistency, meaning that there must be no relevant discrepancy or inconsistency between direct and indirect evidence, such that data must be comparable.[4,5]

Elaborating on the latter, Professor Cipriani explained that if the study population of trial A versus B is not similar enough to that of trial B versus C, the indirect comparison generated will be of little real-world value — even misleading, and potentially damaging. "You can do it mathematically, but it doesn't make sense clinically: you have two different populations, and with the

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SYMPOSIUM

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

Network analysis addresses knowledge gaps in clinical decision making

Continued from page 5

kind of information you have used to link the two treatments it is not a fair comparison."

He further stressed: "Just because it's a network meta-analysis, this does not automatically mean it's good stuff. Absolutely not. Especially now that they have become very popular in the literature, we need to be aware of the risks. Clinicians should be able to critically appraise scientific literature."

He added that, a decade on since the first published network meta-analysis in the field of mental health, its methodology has undergone significant evolution. In collaboration with world class colleagues from academic centres in Europe, US, Canada and Japan, Professor Cipriani's group are now exploring the possibility of applying it along a different plane – for example, comparing pharmacotherapy, psychological therapy, and social or service level interventions. "All of these have different challenges, because of course transitivity and inconsistency are key assumptions," he explained. "We work closely with statisticians and methodologists who are experts in the field. The idea is to develop these approaches to answer clinical relevant questions."

In the comparative study of the efficacy and tolerability of ADHD medications, which Professor Cipriani presents during today's symposium, a number of drugs were considered, including amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil. Included studies were either of drug versus drug or drug versus placebo design, with 12 weeks of follow-up. 133 double-blind randomised controlled trials (81 in children and adolescents, 51 in adults, and one in both) were included. The analysis of efficacy closest to 12 weeks was based on 10,068 children and adolescents and 8,131 adults, while analysis of tolerability was based on 11,018 children and adolescents and 5,362 adults.[1]

Describing its findings, Professor Cipriani noted that some were surprising. In particular, the most safe and effective drug for short-term treatment was found to be methylphenidate for children with ADHD and amphetamines for adults. "This opens up a lot of questions," he commented. "Is it because their brains are different? We don't know why the first-line treatment for younger patients is different from the first-line treatment for adults."

As well as informing the development of clinical guidelines, he suggested that network meta-analyses could also be useful as a basis of discussions between patient and clinician. In the recently published ADHD analysis a league table of sorts is given, ranking drug features alongside other clinically relevant factors, such as side effects. "This is a starting point to discuss with the patient the fact that (for example) if they take this drug, the most likely response rate is X or Y. It's not simply a qualitative judgement – it [becomes] a quantitative discussion.

"[Psychiatry should not be] 'cookbook medicine'. You [cannot] simply scroll down [a list of drugs] from the most to the least effective, because there are many other variables involved."

Facilitating patients' access to informed, quantitative decision-making around their therapeutic choices is something that is more prevalent in other fields of medicine, added Professor Cipriani: "The idea of having a hierarchy of treatment, based on the best available evidence, is something that is done in oncology, immunology, cardiology…why can't we do it in psychiatry?"

> *"The idea of having a hierarchy of treatment, based on the best available evidence; people do this in oncology, immunology and cardiology, so why can't we do it in psychiatry?"*
>
> Andrea Cipriani

Currently, limitations in both data quality and trial methodology to a point hinder the realisation of such possible applications of network analysis. One important limitation in its interpretation lies within the fact that it is usually based on aggregate data: "We are talking about averages and means," explained Professor Cipriani. "We are not talking about individual patients. This is the challenge we are now facing."

> *"We basically build a network of treatment and combine all of the data directly and indirectly to compare each pair of interventions."*
>
> Andrea Cipriani

He proposed that studies using individual anonymised patient data might draw us closer to characterising the effects that a particular intervention will convey in an individual of a certain clinical and demographic background. "That would be a real step towards personalised medicine," he said. At present, data of this kind remains tied up in patient-centred ethicolegal issues of consent and privacy. Negotiations are needed here, said Professor Cipriani: "We need to collaborate with the people who do the trials – authors, industry and registry agencies – who have this data on individual patients, and get access."

The exclusive use of data from randomised controlled trials is also limiting, because of the necessity to select a narrow subset of patients who, for example, are able to give informed consent and do not have certain comorbidities. Such studies are also conducted over relatively short time periods. "The real-world population is different," summarised Professor Cipriani. "Another challenge is to combine randomised and observational data to have a better picture of reality and what happens to our patients."

He added that some regions – such as the UK, Korea and some of Scandanavia – are rich in data and population-based registries in mental health and thus present a unique opportunity for knowledge discovery.

The findings from the recently published ADHD network analysis could also guide future hypothesis design, said Professor Cipriani, with some drugs found to more efficacious or tolerable than others in different age groups. "We need to make the decision, in terms of research, of how to drop these [less effective] medications from the list, to focus instead on the most effective drugs and to try to find better treatments compared to these most effective ones." An alternative, he added, might be to investigate these more effective drugs to identify which patient subgroup, or which symptom, responds best to them. "Possibly, trial design is not [currently?] good enough to detect which subpopulation may benefit from this drug."

Along with the importance of network meta-analysis in providing an evidence-based hierarchy of treatment, the techniques power in filling knowledge gaps is limited: "It is only a partial representation of the efficacy and probability of these interventions," underscored Professor Cipriani in his concluding remarks. "But the important thing is that not all treatments are the same for our patients.

"Our results must be interpreted and contextualised. Patient preferences, the clinical situation, the national situation (e.g. one country may have some drugs that are not available in other countries) – these are all important."

The symposium 'Breakthroughs and controversies in ADHD' takes place this morning between 10:30 and 12:00.

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KEYNOTE LECTURE

Neuroactive steroids as rapid-acting antidepressants… **Friday** 16:30–17:30

Changing the paradigm in depression

This afternoon's keynote lecture will be given by Stephen Kanes, Chief Medical Officer at Sage Therapeutics (Massachusetts, USA), a pharmaceutical company specialising in neurological research. Professor Kanes will be talking about a drug platform that has so far produced the postpartum depression (PPD) drug brexanalone as well as a promising treatment for major depressive disorder (MDD), SAGE-217. Importantly, these two drugs aim to shorten drug treatment times.

During his lecture, Professor Kanes will describe the development programme for brexanolone – the first drug ever specifically approved for postpartum depression – and how that led to SAGE-217. "It's a study of drug development on one level, how we did what we did. It's also a scientific talk looking at the foundations underlying our research. Finally, it's about our data and how these drugs are impactful for the patient," he told *CINP Daily News*.

As the most senior physician responsible for clinical-stage programs at the company, Professor Kanes has overseen the progression of these and other candidate drugs including the clinical design, execution, interpretation and all the aspects of the drug portfolio programme. "We are a neuroscience company with a deep pipeline and a growing opportunity to go after these drugs," he said.

As well as presenting depression data on brexanolone and SAGE-217, Professor Kanes will also explain Sage Therapeutics' approach to drug development for brain health: "Incidentally, these programmes started when we were a much smaller start-up company. Now the company has grown dramatically, and my involvement at a strategic level and scientific level is still hands-on."

Both molecules come from the same research platform looking into neuroactive steroids. "They are very unique," he added.

Brexanolone is an intravenous formulation of allopregnanolone, a naturally occurring neuroactive metabolite of progesterone. It is a positive allosteric modulator of the gamma-aminobutyric acid-A (GABAA) receptor. SAGE-217 is a synthetic drug, based on the same metabolite, but designed with better bioavailability in mind.

> *"We are a neuroscience company with a deep pipeline and a growing opportunity to go after these drugs."*
>
> Stephen Kanes

"With brexanolone, my involvement was strategic from the very beginning – understanding the role of this mechanism potentially and its impact on postpartum depression," said Professor Kanes. "We had known for some time from the basic research that allopregnanolone was one of the hormones that is known to be a trigger for postpartum depression in some women."

At first, Sage Therapeutics looked at the effect of administering allopregnanolone to those women suffering from depression for a brief period of time and tapering it off in a controlled way. "We expected there to be some potential effects, and we were very happy to see the suppression of symptoms," said Professor Kanes. "Two and a half days of infusion resulted in a rapid and sustained improvement in patients with postpartum depression.

"The data was so profound that we decided to use it as a basis for an entire drug development programme[1]." What followed was a series of trials that Professor Kanes will outline in detail during his talk. "What we saw was response rates

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KEYNOTE LECTURE

Neuroactive steroids as rapid-acting antidepressants… **Friday** 16:30–17:30

Changing the paradigm in depression

Continued from page 7

of greater than 70% and full-on remission rates at 50% to 60% without needing additional treatment during the follow-up period."

Such rapid treatment for PPD is virtually unheard of, he noted: "This was a totally different way of thinking about this disorder from a treatment, biological, and most importantly a patient perspective."

In March of this year, the US Food and Drug Administration approved brexanolone for intravenous (IV) use in the treatment of postpartum depression (PPD) in adult women. The success of the drug led the company to look at synthetic versions that possessed a longer half-life, in the hope of enabling patients to take once-a-day dose rather than requiring an IV infusion.

Hence, SAGE-217 was developed. This drug is currently under investigation for a number of other disorders, including major depressive disorder, explained Professor Kanes. "We used brexanolone as a springboard into a medicine that could be more amenable for wider use."

In the recently published double-blind, phase 2 randomised-controlled study of SAGE-217 in 89 patients with major depressive disorder, subjects were randomly assigned to receive 30 mg of SAGE-217 (n=45) or placebo (n=44) once daily. The primary endpoint was the change from baseline to day 15 in the score on the 17-item Hamilton Depression Rating Scale (HAM-D score). Patients assigned to receive SAGE-217 saw a least-squares mean (±SE) drop in HAM-D score from baseline to day 15 of 17.4±1.3 points, while the placebo group score fell by 10.3±1.3 points.[2] "Patients do get better and they get better quickly," commented Professor Kanes. "Not in two and a half days, as in brexanolone, but the therapy showed the same profile overall: a rapid, very large and prolonged effect long after the drug was gone."

Phase III trials are ongoing in the US, with new data expected by the end of this year. A concurrent joint study is being carried out in Asia. "These safety studies will look at how often a person potentially needs to have another treatment, and how long it may take for a patient to require another treatment, if at all," said Professor Kanes. A further study will look at whether there is any effect of the drug on relapse risk, and how patients with treatment-resistant depression react to the drug.

"Our goal is really to take on an entirely new way of thinking of major depression," commented Professor Kanes, adding that a key aim is to provide treatment as needed, rather than antidepressants designed with long-term maintenance administration in mind: "We want to treat patients so that they no longer need to take medicine, until they need it again.

"We want to make drugs that are a step change in the way people are treated."

Stephen Kanes

"We don't want to want to develop the next SSRI or drugs that work in similar ways," said Professor Kanes. "We want to make drugs that are a step change in the way people are treated.

"And for most people symptoms do not return; if they do, it could be years later. There are likely to be many people that only need to treat their depression when it's necessary. Even if you have bouts of depression twice a year, we are talking about four weeks of treatment as opposed to 52. That's why, when you look at our research, it indicates that two weeks is long enough for people to get a maximal response."

"Our goal is really to take on an entirely new way of thinking of major depression."

Stephen Kanes

Looking forward to the next stages of development, Professor Kanes noted that physicians need to be taught how best to make use of a short course depression treatment. Another challenge lies in bringing brexanolone into broad clinical use as an IV infusion: patients must be in an appropriate setting, and they must also be monitored. But facilities enabling this aren't routinely available in the psychiatric setting, and people with PPD are not typically admitted to hospital.

More fundamentally, identifying those with PPD is not easy: "In the US, patients fall through the cracks because there is a lot of stigma. Women have one postnatal visit, and these don't necessarily bring out how they are thinking and feeling. They may not even be referred."

As such, the challenge of expanding access to brexanolone will be also about breaking down stigma. "These are challenges that we expect to take on," said Professor Kanes. "It means that there needs to be adaptation in the overall development of care to accommodate this as new treatment."

He concluded: "It's an exciting time for psychiatry, because there are a lot of new approaches to the treatment of depression. They really represent a shift in the way we may treat our patients in future."

The Keynote Lecture, 'Neuroactive steroids as rapid-acting antidepressants: The story of brexanolone and SAGE-217' takes place at 16:30-17:30 in Olympia Hall today.

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JOURNAL

International Journal of Neuropsychopharmacology (IJNP)

The IJNP covers all aspects related to Neuropsychopharmacology with the central focus on research that advances understanding of existing and new neuropsychopharmacological agents including their mode of action and clinical application or provides insights into the biological basis of psychiatric disorders and thereby advances their pharmacological treatment.

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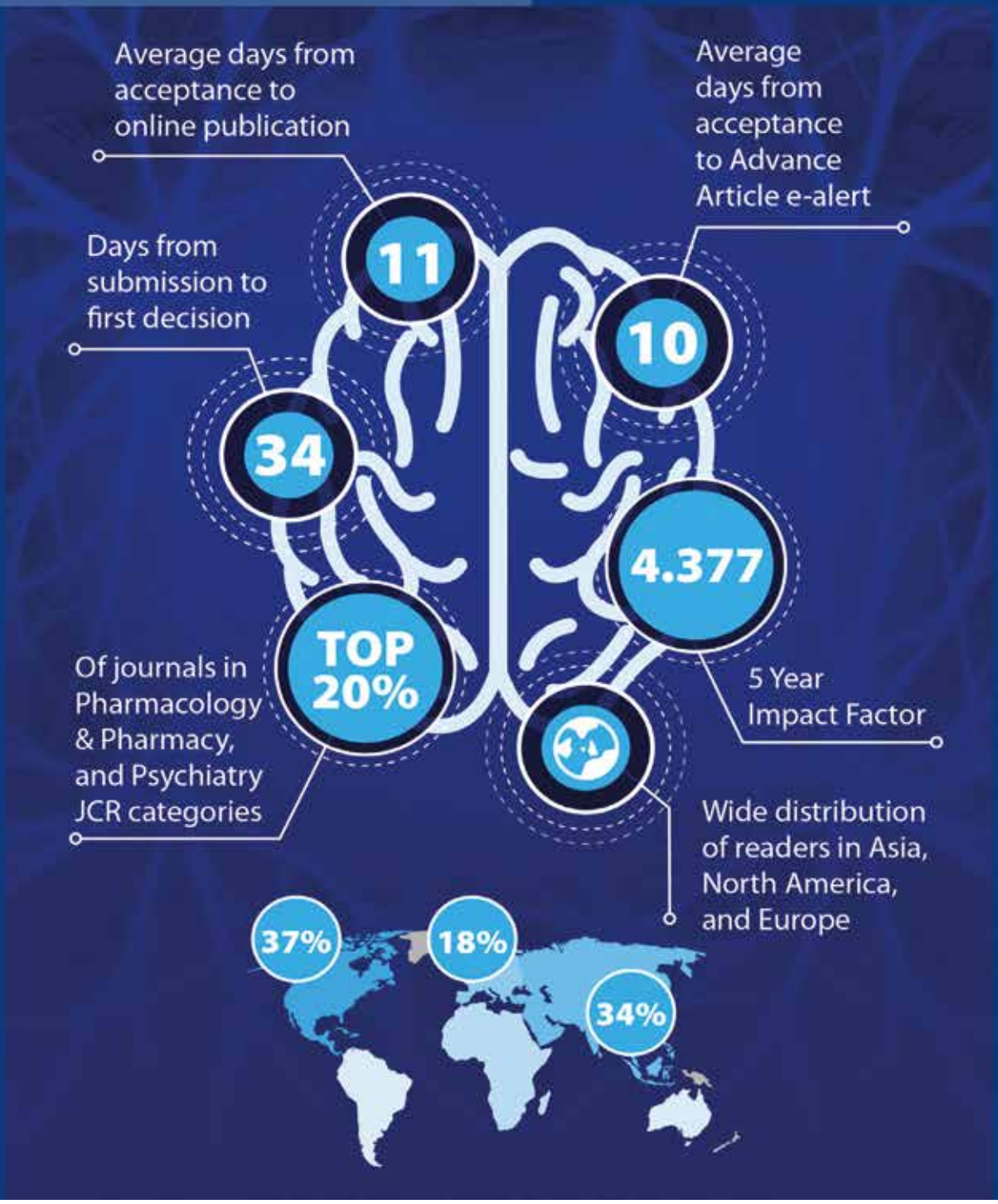

MEET THE EXPERT

Bipolar disorder – the CINP approach **Attica Hall** Friday **10:30 - 12:00**

"A very digital approach"
The development of the CINP bipolar guidelines

In a Meet the Expert session today, Konstantinos Fountoulakis (Aristotle University of Thessaloniki, Greece) describes the CINP approach to guideline development recently employed in the recently published guidelines on bipolar disorder.

The International College of Neuropsychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017) were published in four parts in early 2017[1-4]

As described in the first of these papers, the CINP approach constitutes a strict evidence based approach, with the workgroup arriving at a consensus to base the development of the guideline on randomised controlled trials and related meta-analyses alone. They also conducted a critical analysis of the existing methods for the grading of treatment options, followed by the development of a new grading method.[1]

"This was a unique endeavour," said Professor Fountoulakis, during an interview ahead of the session. "It was the first time that there was such a careful search and interpretation of the data."

The extent of this undertaking is evident in the appendix of part two of the guidelines, wherein treatment treatment modalities are

"This was a unique endeavour."

Konstantinos Fountoulakis

charted against all clinical aspects and options in bipolar disorder. "Essentially, we cut bipolar disorder into pieces, and tried to see which agent works where," commented Professor Fountoulakis.

"The results were that some two-thirds to three-quarters of the cells were empty – meaning that our knowledge is limited. However, we had some very specific guidelines to give on the basis of this spreadsheet; we could say, for example, that if your patient has this specific clinical element, then you will give him or her this agent or treatment. This is a very digital approach. On the basis of this CINP approach – the seek for real knowledge and limiting expert opinion input, to the extent that this can be done – we charted the landscape. The work to develop the guidelines took five or six experts three years."

This also led Professor Fountoulakis and colleagues to develop a mobile phone application, available for iOS and Android. Users can download the app freely, enter the specific clinical features of a patient to find a hierarchical treatment proposal. "Everybody around the world can download it. We hope that it will change the clinical practice of hundreds of thousands of doctors, improving directly, immediately and easily the management and care of millions."

"We cut bipolar disorder into pieces, and tried to see which agent works where."

Konstantinos Fountoulakis

Returning to the guidelines themselves, Professor Fountoulakis noted that, during the process of interpreting the evidence, some surprising findings emerged. "Some things were in very sharp contrast to the expert opinion," he said. "For example, treatment of rapid cycling and mixed episodes is not exactly as expert opinion suggests. Lithium has a role there. Also, lithium seems also to be efficacious in the treatment of psychotic features in acute mania, which was not expected. These are things that need much more research. But still there are hints from the evidence that caught us by surprise."

Professor Fountoulakis speaks during today's Meet the Expert session, taking place between 10:30 and 12:00 in Attica Hall.

The CINP Bipolar disorder treatment guidelines app is available to download from Google Play: https://play.google.com/store/apps/details?id=com.cinp.treatmentGuidelines

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