

# CINP DAILY NEWS

THE OFFICIAL NEWSPAPER OF THE 2019 CINP INTERNATIONAL MEETING

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## CINP 2019 Rafaelsen Young Investigator Award



Bin Zhang

Fredrik Hieronymus

Zheng Chang receives his award from Siegfried Kasper

**O**le Rafaelsen and William Bunney were instrumental in establishing a CINP programme supporting the attendance of young scientists at the XV CINP Congress in 1986. That programme was posthumously named the Rafaelsen Fellowship Award to honour Dr Rafaelsen who died in 1987.

The Rafaelsen Travel Awards enable young researchers to attend the 2019 CINP International Meeting in Athens and mark a step in a rising career.

The award recipients are chosen by an international scientific jury. They also present their posters as part of the scientific programme.

One of this year's winners, **Zheng Chang**, is assistant professor at the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet (Sweden). His research is focused on understanding the risks and benefits of prescribing psychotropic medications, particularly ADHD medications, using large population-based data.

He presented his poster on the association between ADHD

medication and outcomes, using data from the Swedish National Patient Register to find short term beneficial effects of ADHD on several behavioural and psychiatric outcomes.

**Fredrik Hieronymus**, post-doctoral researcher at Aarhus University (Denmark), studies the efficacy and safety of pharmacological treatments for depression, bipolar disorder and psychosis.

His poster presented study showing that the Hamilton Depression Rating Scale measures side effects and therefore underestimates

the antidepressant effect of SSRIs and SNRIs.

**Bin Zhang** is a Junior PI in the Affiliated Brain Hospital of Guangzhou Medical University (Guangdong, China). He researches emotion and cognition interaction and neuropsychopharmacology using functional and structural MRI.

His poster presents evidence that, in patients with MDD with suicidal ideation, response to ketamine is related to blood kynurenine levels before treatment as well as brain activity in the middle temporal gyrus.

## KEYNOTE LECTURE

New Pharmacological Treatments for Resistant Depression **Olympia Hall** Saturday 12:00-13:00

# Resistance is not futile: New pharmacology research making inroads in TRD

New pharmacological approaches for treatment resistant depression (TRD) will be presented on Saturday by keynote lecturer Maurizio Fava, psychiatrist-in-chief at Massachusetts General Hospital (MGH). Professor Fava is also director of the clinical research division at the MGH Research Institute, executive director of the MGH Clinical Trials Network and Institute (CTNI) and Slater Family Professor of Psychiatry, Harvard Medical School.

Speaking to *CINP Daily News* ahead of his lecture, he described the current research landscape: "It's an exciting time to be in clinical neuroscience with all these new targets. Many classes are being researched and have emerged in the last five to ten years."

Professor Fava founded and was the former director of the depression clinical research programme at MGH from 1990 to 2014. It was here that he first helped to establish the need for effective drugs for the treatment of TRD.

He was also one of the three principal investigators in the STAR<sup>3</sup>D

trial, the largest and most consequential antidepressant study ever conducted<sup>1</sup>. The trial enrolled 4,041 patients who screened positive for major depressive disorder (MDD) while seeking routine medical or psychiatric care. "In that study, we found that patients who don't respond to one or two antidepressant drugs end up having very low chances of responding to subsequent attempts with antidepressants alone," Professor Fava summarised.

The reason for this, he proposed, is that currently available antidepressants are all monoamine-based, and therefore operate in broadly similar ways. "You could try many different ones, but in the end you have to start looking for other avenues to get people to respond," he explained. "I believe that you need to think about augmentation and adding drugs with different mechanisms that are not monoamine based."

In his keynote, Professor Fava will outline a number of alternative treatments that are either available or in development. Crucially, all are

showing some activity against TRD, and many are under study in clinical trials by Fava and his group.

One avenue under pursuit is treatment augmentation with dopaminergic modulators, a class of drugs that includes dopamine reuptake inhibi-

*"There are lots of new exciting targets and new tools although we need studies to guide us for a more precision medicine approach to their use."*

Maurizio Fava

tors, dopamine agonists and atypical antipsychotics. The latter is the most promising, said Professor Fava: "Atypical antipsychotics affect a number of systems, are multi-action drugs and have the best evidence of efficacy."

Currently, three drugs are approved in the US for augmentation: aripiprazole, quetiapine and brexpiprazole. Other atypical antipsychotics, such as cariprazine, have also been studied for resistant depression and have shown some activity too.

The second group of drugs that show activity are those able to modulate brain bioenergetics via the modulation of mitochondrial activity<sup>2</sup>.

Neurogenesis-promoting agents are also proving of interest. Studies of buspirone in combination with melatonin show a vast increase in neurogenesis, known to be significant in the alleviation of depression<sup>3</sup>. Similar findings have surfaced with regard to NSI-189, a compound in development<sup>4</sup>.

Modulation of the immune system presents a further option for combating TRD, added Professor Fava: "There is a clear relationship between depression, stress and the immune system<sup>5</sup>. That is why compounds such as S-adenosyl-L-methionine (SAME) (naturally found in

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## Programme: Thursday 3 October

08:30

09:00

09:00 - 10:00

**Keynote Lecture**

**Interactions between neurotransmitters: the key to remission in depression**

09:30

*Pierre Blier*

10:00

10:00 - 10:30 **Coffee Break**

10:30

10:30 - 12:00

**Symposium**

**Future directions to understand psychiatric diseases**

11:00

*Konstantinos Pastiadis, Georgia*

11:30

*Salanti, Hans-Jürgen Möller*

12:00

12:00 - 13:00

**Keynote Lecture**

**New Pharmacological Treatments for Resistant Depression**

13:00

*Maurizio Fava*

13:30

13:00 - 13:30 **Closing**

14:00

13:30 - 14:30

14:30

**Lunch**

10:30 - 12:00

**Meet the Expert**

*Sponsored by Takeda / Shire*

10:30 - 12:00

**Workshop**

*Erich Seifritz*



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the body), omega-3 fatty acids or the phosphodiesterase inhibitor pentoxifylline (which has anti-inflammatory effects) have all shown a benefit in depression as augmentations. The 17 antibody Ixekizumab has shown benefits. This is a high-affinity monoclonal antibody, targeting interleukin 17a.”

Another promising set of treatments are those that target  $\gamma$ -aminobutyric acid (GABA) and glutamine. In September of this year, a study of SAGE-217, an oral, positive allosteric modulator of GABA type A receptors, has demonstrated a robust anti-depressive effects in phase II trial. It was found that the administration of SAGE-217 daily for 14 days resulted in a reduction in depressive symptoms at day 15. Adverse events were more common, however, in the SAGE-217 group than in the placebo group, suggesting that further studies are necessary.<sup>6</sup>

Similarly, studies are targeting glutamate activity in depression: “Ketamine, which is a glutamate NDMA receptor antagonist, has shown very robust efficacy,” continued Professor Fava. The same can be said for intranasal esketamine, which won approval from the US Food and Drug Administration (FDA) to be used in conjunction with an oral antidepressant for the treatment of TRD in March this year.

Despite its activity against TRD ketamine remains a contentious drug, concedes Professor Fava: “Perhaps other delegates at the conference might be surprised by the use of ketamine and even esketamine, because of the potential for abuse,” he said. “There may also be some controversy with psychedelic drugs that are active against TRD.”

Indeed, earlier this year, the first results of the controlled trial to test a psychedelic substance, ayahuasca, in TRD suggested adequate safety and therapeutic value if administered within an appropriate setting.<sup>7</sup>

There are a wealth of alternative candidates acting upon glutamate that show promise or are under study. Rapastinel (GLYX-13) and basimglurant, a negative allosteric modulator of the mGlu5 receptor, are among several candidates, noted Professor Fava. Other glutamatergic compounds include pregabalin, CP 101606 (Pfizer, US), D-Cycloserine and memantine, he added. In addition, quinidine mixed with dextromethorphan, an NMDA receptor antagonist, for example, and dextromethorphan/bupropion have also shown activity in depression.

The last drug group that Professor Fava will discuss is that modulating the opioid system. Promising molecule



Maurizio Fava (left)

*“There are lots of new exciting targets and new tools although we need studies to guide us for a more precision medicine approach to their use.”*

Maurizio Fava

ALKS 5461 (buprenorphine plus opioid receptor antagonist samidorphan) has been the focus of the FORWARD-4 and FORWARD-5 trials<sup>8</sup>. This is a once-daily oral combination of samidorphan and buprenorphine.

Looking forward, there may be many options emerging for those with TRD, said Professor Fava. “The bottom line of my presentation is that the dopaminergic modulators are showing efficacy. GABAergic and glutamatergic drug treatments have robust evidence of efficacy in TRD, in particular esketamine. Neuroinflammation in MDD has become an important target for the development of new therapies and anti-inflammatory agents show real promise.

“In addition, mitochondrial and bioenergetic abnormalities in MDD suggest the usefulness of strategies increasing brain energy metabolism. Neurogenesis-promoting and opioid modulating compounds appear to be promising therapies for depression.”

Most candidates are still under development, he added, while others are already on the market but not currently indicated for TRD: “Because these don’t have an approval specifically for depression – at least in the US – we are allowed to prescribe them but the issue is whether or not the insurance will cover the off-label use.”

A crucial need is for more direct comparisons between treatments, he said: “There has been no head-to-head study comparing these newly available compounds. We did it 15 years ago with the old compounds. There’s a clear need for [similar] study with newer treatments.”

Despite these needs, concluded Professor Fava, the present topology of research provides ample reason to be positive: “There are lots of new, exciting targets and new tools, although we need studies to guide us for a more precision medicine approach to their use. This is an exciting time to be a practising psychiatrist.”

Professor Fava’s Keynote Lecture, ‘New Pharmacological Treatments for Resistant Depression’ takes place on Saturday at 12:00-13:00.

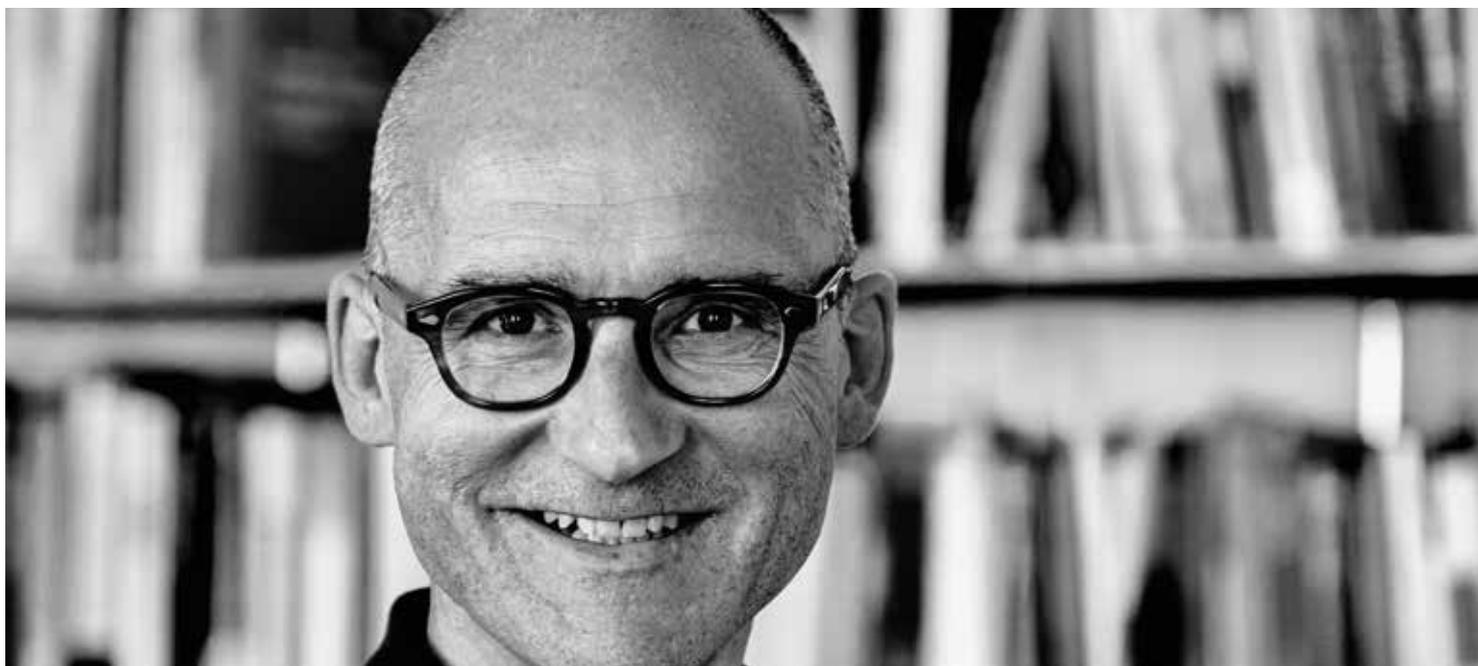
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## WORKSHOP

Depression – new treatments with psychedelics **Attica Hall** Saturday 10:30–12:00

# Back from the wilderness: the latest in psychedelics research



**E**rich Seifritz, chairman of the Department of Psychiatry, Psychotherapy and Psychosomatics at the Psychiatric Hospital, University of Zurich will hold a workshop this morning on the renewed interest in the potential clinical benefits of psychedelics in treating depression.

“Personally, I see great potential in the combination between this drug class and behavioral treatments,” Professor Seifritz told *CINP Daily News*.

His department has been researching psychedelics, as well as other treatments, for many years. “Our main research strategy is translational and heads towards the development of innovative experimental antidepressant treatments.”

Professor Seifritz will give a historical overview of psychedelics research, illustrating as he does so how this field is a far cry from what it was decades ago: “I am not talking about the psychedelic treatments that were employed during the 1960s,” he explained. “I am talking about neuroscience guided pharmacotherapy that addresses specific functional cognitive, emotional and behavioral domains that are relevant for psychotherapy, e.g. memory functions.”

In providing an overview of the evolution of pharmacological treatments for depression, he will also show that most current antidepressants essentially act in a similar way mechanistically. “This is the fundamental problem,” he said. “All the drugs we have available are more or less similar. So we cannot really expect a fundamental difference in the efficacy of this group, because within it, there is so much resemblance between one drug and another.”

One of the most striking differences between classic antidepressants and psychedelics is their rapidity of action. Classic antidepressants may take

*“I see great potential in the combination between this drug class and behavioral treatments.”*

Erich Seifritz

10 days, two weeks, or even longer to reach a measurable clinical effect. In psychedelics, this can be almost instantaneous, said Professor Seifritz: “We see a change in minutes, or even a couple of hours. Clearly, there must be a different mode of action or neurobiological mechanism behind how these differences in time constants evolve.”

Specifically, the antidepressant effects of psychedelics seem to rely on different molecular and circuit-based mechanisms than classical serotonergic and adrenergic antidepressants. “There must be mechanisms involved that produce reorganisation of connectivity in the brain. Of course, these effects are incompletely understood. But that is why the whole community is really excited about the psychedelics.

“Our department has continued to conduct research very systematically,” said Professor Seifritz. “We really don’t fully understand the principles of how these drugs work. There are several hypotheses.”

The several classes of psychedelics, grouped into the serotonergic, glutamatergic and GABAergic, will be outlined by Professor Seifritz during his talk.

The best-known psychedelic and most advanced in terms of entering clinical practice

is the NMDA antagonist ketamine. Its isomer esketamine has already been approved for use in treatment resistant depression in the US. “The intranasal application of esketamine has even been proven effective in large randomised clinical trials,” commented Professor Seifritz. “It is being registered for the treatment of treatment-resistant depression in different countries.”

The interest in ketamine began some 15 years ago when a group of researchers from Yale University in the US published an open-label small clinical study showing that a short infusion with ketamine in treatment resistant depressed patients had a strong and fast antidepressant effect. “They could observe the antidepressant effect within an hour. That was almost incredible,” said Professor Seifritz. “The peak of the effect was observed 24 hours after the infusion.”

The serotonergic psychedelics, such as psilocybin and lysergic acid diethylamide (LSD), also offer therapeutic potential. Psilocybin is a classic hallucinogen naturally occurring in more than 100 species of mushrooms worldwide. LSD, said Professor Seifritz, is not particularly well understood and is far from being incorporated into clinical practice. “Psilocybin is better understood. It is much more advanced in clinical testing in patients regarding changes and effects in depression symptoms. I will present human data from our group about neuropsychological and neurophysiological effects of psilocybin which produce a clinical effect that is useful for the treatment of depression. I will also show some new data of the molecular and brain region characteristics of LSD in normal humans.”

Human research on LSD neurobiology stopped decades ago for a number of reasons. While knowl-

*“It is time to develop antidepressant medication that goes beyond the classical monoaminergic mechanisms.”*

Erich Seifritz

edge gaps in the understanding of its pharmacology and effect on cortical connectivity persist, recently renewed research efforts have made inroads in elucidating these. Indeed, Professor Seifritz co-authors a recent paper demonstrating that LSD significantly impairs executive functions, cognitive flexibility, and working memory, with a methodology hinging on previous efforts evidencing the compound's agonistic action at 5-HT<sub>2A</sub> receptors<sup>2</sup>.

In other recent imaging study, he and others found evidence supporting the notion that the disintegration of information processing within cortico-striato-thalamo-cortical (CSTC) feedback loops underpins LSD's psychedelic properties.<sup>3</sup>

Professor Seifritz also will discuss research into other psychedelics with antidepressant potential during his workshop, including the preclinical effects of gamma-hydroxybutyric acid (GHB), and the drug development programme of ayahuasca.

The already established place of some of these substances on the recreational drug scene is reason for caution, highlighted Professor Seifritz. While ketamine can be used for anaesthesia in higher doses, it is also a drug of abuse favoured for its

dissociative effects. “Because of its abuse potential, ketamine should be employed in specific settings only to treat treatment-resistant depression,” he advised. “These include a protected environment to accompany the patient when dissociative side effects should occur. These are transient but require patient care. In addition, to prevent abuse, ketamine should not be placed at the disposal of the patient like other antidepressants.”

Indeed, in rare cases patients have experienced transient blood pressure increase after ketamine administration intravenously or intranasally, noted Professor Seifritz, adding: “Although acute physical problems are extremely rare, patients should stay under medical observation for an hour or so, according to the regulator's provisions.”

Better understanding of the mechanisms underpinning psychedelics' antidepressant effects is crucial in their therapeutic development. “If we do this, it will eventually become possible to design antidepressant drugs in the future that produce the desired positive effects, but not the current side effects.”

He added further as-yet unanswered ques-

tions: “How long should successful psychedelic treatments be maintained after clinical symptom improvement? What are the ideal doses and application regimens? And can we develop biomarkers that predict which patient will respond to ketamine and which patient will not?”

Professor Seifritz concluded by stressing the demand for new therapies for patients whose needs aren't being met: “It is time to develop antidepressant medication that goes beyond the classical monoaminergic mechanisms. Psychedelics appear to be promising candidates.”

The workshop ‘Depression – new treatments with psychedelics’ takes place in Attica Hall today between 10:30 and 12:00.

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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)



*“The interactive presentation is very good”*

Attendee of the ‘Discovering ADHD in Adults’ Session, ECNP 2019

### 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

## KEYNOTE LECTURE

Oldřich Vinař Keynote Lecture: Treatment resistant depression **Olympia Hall** Friday **09:00 - 10:00**

# The Oldřich Vinař keynote lecture

Despite consistent advances in pharmacotherapy of mood disorders in the last decade, high rates of treatment resistant depression (TRD) remain a challenge of clinical management. This formed the basis of a keynote lecture delivered yesterday morning by Siegfried Kasper, who outlined the key findings of European study in this area.

## In memory of Oldřich Vinař

Professor Kasper began his lecture with a few words in memory of the lecture's namesake.

"This lecture is devoted to my good friend, Oldřich Vinař, who probably some of you know. Unfortunately he died last year, and the executive committee decided to give him special note in this meeting.

"He was born in 1925 and died in 2018 at 93 years old. Original from Brno, he went on to Prague and was very eminent in fostering neuropsychopharmacology not only in the Czech Republic but also throughout Europe and worldwide. In those days it was not so easy to develop the neuropsychopharmacology. One of his greatest achievements was founding, in 1958, the meeting in Jeseník (on the Czech-Polish border) and for over 60 years this has been a very prosperous meeting. He was working in the

Czech research institute, was a member of the WHO Czech centre, and he worked with international colleagues.

"He developed a number of tests before the introduction of the Brief Psychiatric Rating Scale or the Hamilton score, and he used them as neuropsychopharmacological research tools. In 1968, he was accepted into the American College of Neuropsychopharmacology (ACNP), when the Russians moved into Czechoslovakia. This was quite an achievement; it was due to his very good reputation.

"He published a number of good papers. He was one of the forefathers of the D2-5HT<sub>2</sub> blockers. The only problem was that he published in the Czech language, in the *Czech Journal of Neuropsychopharmacology* (which he also founded), so he is not referenced that often compared to our other colleagues.

*"I personally think that hippocampal structure with network connectivity should be used in clinical practice."*

Siegfried Kasper

"What I also valued very much about Oldřich is that I saw him at all different kinds of meetings until he got very old. At the last ACNP meetings, he always came with his grandchildren."

## Therapy-resistant depression: A clinical approach

Professor Kasper continued to address the lectures theme: "When we talk about TRD, it is important that we view it also as a brain disease – of course, a brain disease that reaches out to the psychosocial environment and has all different implications," he began, before presenting some of the main findings of European studies of TRD, alongside clinical insights emerging therefrom.

Professor Kasper suggested that confusion in clinical terminology of TRD – which can be referred to varyingly in the literature with terminology such as 'difficult to treat depression', 'refractory depression', amongst others – ought to be reconsidered, given that it is an indication for a very specific treatment. "We should instead be talking about stages, and these stages should include patient characteristics, illness characteristics, and treatment history.

"Where are we today? We know from different studies that the second and third treatment is associated with worse outcome; this is a medical principle in different parts of medicine...the 'wait and see' mentality is very bad, based on the data we have available. We know from different studies that augmentation is better than switching. That was one of the major outcomes (from my point of view) of STAR\*D and other studies. We know that without remission, recurrence is common. Partial remission is associated with a delay in access to effective treatment."

He then described the work of the European Group for the Study of Resistant Depression (GSRD), with centres in Belgium, Paris, Switzerland, Italy, Germany, Athens and Tel Aviv. Over almost 20 years, the GSRD have collected 2,764 patients recruited in both university and non-university centres. These patients represent a real-world sample of depressed patients seeking treatment, exhibiting a broad range of disease severity and course as well as mental and somatic



Oldřich Vinař

comorbidities and suicidality. GSRD has carried out cross-sectional clinical evaluation of patient characteristics and illness characteristics, and they will soon be incorporating genetic parameters into their study. A summary of the group's clinical, genetic and pharmacological findings to date, which has fundamentally impacted evidence-based algorithms for diagnostics and psychopharmacotherapy of TRD, has recently been published<sup>2</sup>.

A key recent finding of the group is of the clinical factors predicting TRD, which include comorbid anxiety disorder, suicide risk, symptom severity and number of major depressive episodes<sup>3</sup>. Indeed, STAR\*D showed, in a cohort of patients assigned to the SSRI citalopram, that remission was less likely and took more time in patients with depression and anxiety<sup>4</sup>.

*"What I valued very much about Oldřich is that I saw him at all different kinds of meetings until he got very old."*

Siegfried Kasper

In a recent study by Dold et al (2018), patients with TRD had significantly higher suicidality scores compared to patients who responded to treatment<sup>5</sup>. "Very often, we are so overwhelmed by the psychopathological symptomatology of suicidality that we do not think about the treatment resistance," commented Professor Kasper. "But treating these patients effectively from the first stage on is quite important."

Turning to the lessons learned from the GSRD on prescription strategies in MDD, he cited Dold et al (2016), who found that 53.4% of patients were prescribed SSRIs as a first-line treatment, and 23.6% SNRIs. The authors also looked at



additionally prescribed medications, finding benzodiazepines and related drugs most likely to be given (33.2%), followed by a second antidepressant (29.0%), antipsychotics (24.2%), and mood stabilisers (10%).<sup>6</sup> In later work, Dold et al (2018) found second generation antipsychotics superior to lithium as augmentation treatment<sup>7</sup>.

Professor Kasper also highlighted recent work from Mandelli et al (2019)<sup>8</sup>: “Usually it is thought that if you have a low occupational level, you have a higher likelihood of becoming treatment resistant. In this study, and also in other independent study, we found that higher occupational levels are associated with treatment resistance. Two reasons are discussed: first, that for higher occupational level you need cognition, and cognition is impaired in our patients; second, if you have higher occupational level, probably you have more possibilities to choose other types of medications that have not been proven to be effective.”

He characterised unmet needs in the treatment of patients with MDD, including a lack of biomarkers, a lack of understanding of risk factors and outcome predictors, and a lack of effective treatments with quick onset of action and sustained efficacy.

Addressing the development of precision medicine in psychiatry,

he said, “We are not there yet. But on the other hand we have some data. We published a paper on the genetic polymorphisms and clinical parameters, and found inflammatory parameters together with brain-derived neurotrophic factor polymorphisms and melancholia to be linked together as one of the predictors<sup>9</sup>.”

Neuroimaging parameters in MDD have also recently been reviewed (Kraus et al, 2019)<sup>10</sup>, and Professor Kasper commented on this work: “I personally think that hippocampal structure with network connectivity should be used in clinical practice. Quite often we send a patient for an MRI [to investigate] tumours or brain atrophy, but nobody measures the hippocampus. We psychiatrists have to measure them ourselves. We have the machinery.”

He added that Kraus et al (2019) also outline a sequential treatment optimisation paradigm for selecting first-, second-, and third-line treatments for acute and chronically ill patients<sup>10</sup>, suggesting: “This is a staging model that I think could enter clinical practice.”

In their review, Kraus et al (2019) also specify easily overlooked but modifiable factors potentially confounding response to antidepressant treatment. These include checking the

dosage and duration of trial, reducing side effects, treating comorbidities, reducing ongoing stressors, considering pseudoresistance, conducting pharmacogenetic testing (e.g. of CYP450),

*“We should instead be talking about stages, and these stages should include patient characteristics, illness characteristics, and treatment history.”*

Siegfried Kasper

checking medication interactions, starting illness-specific psychotherapy, and evaluating initial dosing<sup>10</sup>.

Professor Kasper concluded the session with a discussion of the latest developments in drug discovery in TRD, including ketamine (discussed in detail on p8-9 of this issue of *CINP Daily News*).

Commenting on the landscape of antidepressant evolution, he said: “We made a major step forward moving from the tricyclics to the SSRIs and SNRIs. I think we have good medication – the old medications work quite well – but we also need advancement in our field.”

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## WORKSHOP

Neurobiological and clinical characterization approaches...forTRD **Templar's Hall Thursday 13:00 - 14:30**

## Workshop brings together great minds in TRD research

Jennifer Evans and Bashkim Kadriu were panelists in Thursday's workshop on the neurobiological and clinical characterisation approaches for developing novel therapeutics for treatment-resistant depression (TRD). Ahead of the meeting, the pair spoke to *CINP Daily News* to discuss the session as well as their own work.

The workshop brought together four different perspectives in tackling TRD with the aim of informing attendees of the latest effort in trying to apply neurobiological and clinical characterisation approaches for the development of novel therapeutics in TRD.

Dr Evans is a Staff Scientist at National Institute of Mental Health (at NIH) (Bethesda, Maryland). Her interests lie in applying imaging methods, particularly functional magnetic resonance imaging (fMRI), to clinical questions. She is currently investigating the fMRI response after intravenous ketamine administration in relation to behavioral changes in subjects with major depressive disorder (MDD) and healthy controls.

Dr Kadriu is a board-certified psychiatrist and neuroscientist at the Experimental Therapeutics and Pathophysiology Branch (ETPB), National Institute of Mental Health (NIMH). His research interests include the neurobiological correlates of treatment-resistant mood disorders, with a particular emphasis on discovering biosignatures that guide novel fast-acting antidepressant actions.

"My work focuses on metabolomic approaches to characterise treatment response to ketamine in TRD patients," explained Dr Kadriu. Dr Evans added: "I'm going to be talking about trying to find imaging markers of response in TRD."

The session opened with a presentation from Christoph Kraus, whose research included translating functional MRI (fMRI) biosignatures into clinical care settings. Zhi-De Deng spoke about reinventing ECT to optimise various aspects of its dose delivery and individualisation in order to minimise its side effects in patients with TRD.

The session concluded with some perspectives from Carlos Zarate (NIH), a world renowned expert in the field, providing an overall picture of the present state of the neurobiology of depression and novel therapies, as well as insights into how the field of

depression is evolving.

The definition of TRD remains a matter of some debate, explained Dr Kadriu: "This is probably one of the really relevant questions in the field. One of the classic definitions is a failure of clinically meaningful improvement and non-response to two consecutive standard antidepressant treatments used sufficiently enough in length, with adequate dose and adherence."

A number of groups have developed approaches to staging the level of resistance in TRD. These include the Thase and Rush Staging Method<sup>1</sup>, the Massachusetts General Hospital (MGH) Staging Model<sup>2</sup> and the Maud-

*"Ketamine seems normalise network dysfunction."*

Jennifer Evans

sley Staging Method<sup>3</sup>.

At the NIMH, this patient population is highly treatment resistant: "Our recruited sample have on average failed at least seven to eight different psychotropic medications," said Dr Kadriu, "And roughly 50-70% of these patients have failed ECT before coming to us."

The group study this patient cohort in order to build an in-depth library of individual neurobiology and clinical characteristics. Dr Evans described the work that she is currently doing to achieve this goal: "We are trying to get a good handle on the heterogeneous landscape in MDD from the imaging perspective."

"Several putative markers are being investigated. In structural MRI, regions of the brain have been found that might be reduced in depression, such as hippocampal volume. This has been shown in a very large sample – the ENIGMA cohort. We are looking at this marker."

"We are looking at functional markers with fMRI, magnetic encephalography (MEG), and you can study network dysfunction in MDD as compared to healthy controls. We



have studied different networks – for example, the default mode and cortico-striatal network and the response to ketamine. Ketamine seems normalise network dysfunction."

Her investigations also extend to magnetic resonance spectroscopy (MRS) in the study of glutamate in depression<sup>4</sup>:

"We are trying to understand metabolic dysfunction in depression this way. We are trying to use this constellation of approaches in order to find markers that characterise depression."

Dr Kadriu then turned to the ongoing investigations into molecular biosignatures in depression, citing the work of Robert Innis (NIMH) into new and promising PET radioligands such as translocator protein (TSPO) that could soon be used in the clinical setting to characterise the neuroinflammatory state of the brain. Dr Innis's group have recently shown that TSPO is

increased in unmedicated MDD patients with respect to medicated patients and healthy volunteers<sup>5</sup>. "What is interesting is that this study inspired a number of other independent studies, with five out of six of them confirming these initial findings that were produced in collaboration with Dr. Zarate group," commented Dr Kadriu.

Research approaches such as this reflect a growing acknowledgment that clinical metrics based on staging that incorporate the number of failed drug treatments alone are not sufficient to characterise TRD. Instead, explained Dr Kadriu, clinical (length of illness, number of hospitalisation, previous suicidal behaviors, etc.) and biological correlates (obtained from imaging, sleep and peripheral and central biomarkers) should be centerpiece of future TRD characterisation efforts.

Explaining how her research is contributing to this, Dr Evans explained: "We try to take an in-depth look at each of our patients. We put them through multimodal imaging – at 3T and at 7T with structural and functional MRI – in order to get a

*"You have to take a multifaceted approach using cross-modality integration."*

Jennifer Evans



deep characterisation of the disease in each of our patients.

“We also do a number of clinical studies on new drugs, as well as ketamine. Here, we image at multiple time points in order to characterise response for each of these drugs. Eventually, we aim to find several markers that we will be able to use to predict response for each of these people for any given drug.”

She summarised: “From my perspective in my work on TRD, in trying to identify and develop new antidepressants you have to take a multifaceted approach using cross-modality integration. You also have to work across multiple fields, bridging psychiatry with imaging, in order to best address the heterogeneous response.”

The recent FDA approval of esketamine has cementing its place on the clinical psychiatry landscape, as much as it has influenced current and future research directions in depression. Yet the drug holds potential benefit in a range of psychiatric disorders, explained Dr Kadriu: “One of the striking facts about ketamine is that it appears to have what we call a pan-therapeutic effect, in a similar

*“The approval of three new treatments for the treatment of depression over the course of a single year is a singular achievement.”*

Bashkim Kadriu

timeframe as it does in depression, in modalities such as anhedonia, fatigue, sleep and most importantly acute suicidal thoughts. This is of critical importance, as suicide strikes across different psychiatric disorders including depression, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), etc.

“Recent studies show that a single dose of ketamine appears to be effective in, for example, obsessive compulsive disorder, PTSD and bipolar depression. It seems to have a seemingly robust effect, similar to that seen in MDD. Researchers are trying to understand the long term repeated effects of ketamine in patients with depression and relating this to how it

*“The field is really puzzled as to why we are not able to ‘sanitise’ the side-effect profile of [ketamine] while retaining its treatment effects.”*

Bashkim Kadriu

impacts the brain.”

The recent FDA approval of its derivative esketamine for adults with TRD and the recent approval of brexanolone for postpartum depression (PPD)<sup>6</sup>, with an oral analogue currently under trial for MDD, signify the first mechanistically novel and distinct antidepressant agents to appear in decades. Theta burst stimulation (TBS) has also been recently approved recently by the FDA for depression.

“The approval of three new treatments for the treatment of depression over the course of a single year is a singular achievement,” summarised Dr Kadriu. “It highlights the possibility of developing urgently needed next-generation treatments based on an improved understanding distinct

from the historical monoaminergic-based treatments that takes weeks to months to show meaningful clinical improvement in depression.”

Despite tremendous progress, challenges have arisen in the investigation of many novel, promising and rapid-acting (as well as non-rapid-acting) antidepressant interventions for depression. Ongoing work seeks to address some of the dissociative and psychotomimetic side effects of ketamine. As yet, trials with ketamine-like agents that have shown promise in preclinical setting (such lanicamine, GLYX-13 and AV-101) have failed to meet primary study endpoints in human studies (as recently summarised by Duman (2018)<sup>7</sup>).

In his concluding remarks, Dr Kadriu considered what might make ketamine unique: “It is, conceptually, a ‘dirty’ drug,” explained Dr Kadriu. “It acts upon so many different receptors, which might be one of the factors making this treatment unique. The field is really puzzled as to why we are not able to ‘sanitise’ the side-effect profile of the drug while retaining its

treatment effects.”

Ongoing collaborations with extramural programmes -- such as that of Todd Gould’s group at the University of Maryland -- into the dozens of downstream metabolites of ketamine seek to do just this: “An example of that is 2R,6R-hydroxy-norketamine (known as HNK), which in preclinical animal models of depression appears to retain the rapid and sustained antidepressant-like actions of ketamine but is devoid of its dissociative-like properties. This is achieved in part via the potentiation of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA)-mediated synaptic transmission<sup>8-10</sup>,” Dr Kadriu said in closing.

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## SYMPOSIUM

Future directions to understand psychiatric diseases **Olympia Hall** Saturday 10:30-12:00

## “Evidence does not equal evidence”

During this morning's symposium on the future directions in understanding psychiatric disease, Hans-Jürgen Möller (Ludwig-Maximilians-University, Germany) discusses issues related to the development of evidence based guidelines, illustrating as he does so that grading of evidence is neither simple nor objective.

“Evidence is the magic word nowadays,” he commented ahead of the session. “You find it in all guidelines and in all things related to decision-making in clinical psychiatry and clinical medicine in general. ‘Evidence’ means that you put together all of what is known from randomised controlled studies or from other methodologically sound studies.”

While this seems a straightforward concept, he explained, the way that evidence quality is rated is susceptible to variation due to differences in approach, criteria and judgement: “Everybody can summarise the final result or final content of all studies made in the specific or related area, in different ways.”

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, for the rating and summarising of quality of evidence supporting management recommendations, emerged in 2004<sup>1</sup>. It was revisited in a 2008 series of BMJ papers summarising its important methodological features, including those that factors that inform decisions on evidence quality for better or worse.<sup>2</sup>

One persistent dilemma, noted Professor Möller, concerns study selection and in particular whether to base evidence assessments on individual studies of high methodological standard or metaanalyses. On the one hand, review of individual studies provides direct and concrete insights into trial data relating to a particular question in clinical management. But while they avoid the abstraction that occurs in metaanalysis, individual studies remain prone to selection bias. In addition, given their nature, randomised controlled trials do not reflect real world clinical complexity.

Metaanalyses carry their own set of issues, with bias coming from study selection criteria (with the added possibility of including studies of varying quality), data extraction strategies, statistical strategies, as well as over-generalisation from the consideration of small-scale studies.

“To do metaanalysis is a bit tricky,” noted Professor Möller. “You can perform metaanalyses in different methodological ways. This can then lead to the problem that metaanalysis X leads to a different conclusion than metaanalysis Y. This is due to the different method — and not due to different data.”

Drawing these factors together, Professor Möller summarised that evidence, and evidence grading, are not as consistently defined as may be believed. Indeed, there are a number of different systems of

*“Evidence level A should not be taken as some sort of [absolute metric], like a centimetre, but as a totally relative measurement.”*

Hans-Jürgen Möller



evidence grading currently in use, with no international consensus on the matter. Different guidelines place either individual study data of high methodological standard or metaanalysis upon the highest rung of quality. The outcome of this, he said, is that different authorities come up with different recommendations — and clinicians should be aware of this. “If you find in the guideline that a certain treatment (e.g. compound X) is better than another (e.g. compound Y), with an evidence of level A, you might find in another guideline that there is no clear difference at all, or that the difference is very small and that the evidence is only of level B or C. We are talking, principally, about the same database, but different data selection, different kinds of metaanalysis, etc.”

He added a further conclusion: “Evidence A is not equal to evidence A in another guideline, because in a certain guideline they might look primarily at individual studies and calculate the positives and negatives of these studies, while the other guideline is doing a metaanalysis. Therefore, evidence level A should not be taken as some sort of [absolute metric], like a centimetre, but it is a totally relative measurement.”

He also noted the incomparability of drug versus psychotherapeutic treatments in metaanalysis, given the tendency of drug trials to be double-blinded,

randomised and controlled, while psychotherapy trials are less likely to be so.

Elaborating on exactly why it is problematic that different guidances take different stances on particular questions, Professor Möller explained that this can lead to conflict between treatment guidelines and drug authorities. The authors of the 2017 CINP guidelines on bipolar disorder summarised the differences in recommendations as compared to other current guidances, and Professor Möller will discuss these differences in depth during his talk: “We found out that in some areas — for example, in the treatment of bipolar depression — there are quite relevant differences concerning the compounds that are suggested,” he said.

“In contrast to several other guidelines, which focus their decision making on metaanalyses, the CINP guidelines on the treatment of bipolar disorder primarily focus on individual trials, for good reasons. In comparison to the recommendation of some other guidelines, the CINP guidelines show a lot of similarities, but also some differences. But they are more detailed when it comes to, for example, individual syndromal aspects.”

Professor Möller speaks during ‘Future directions to understand psychiatric diseases’, taking place in Olympia Hall at 10:30–12:00 today.

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