ECNP Experimental Medicine Network

Validating new biomarkers for unmet needs in the management and treatment of depression - Meeting 2

Frankfurt, 26-27 June 2023

Meeting Minutes

SESSION 1 – 26 JUNE 2023

Introduction and welcome

Chair: Gerry Dawson

Review of Meeting 1 and Overview and objectives for Meeting 2 - Gerry Dawson

Gerry Dawson (GD) provided a review of meeting 1 and summarized some of the topics discussed at the previous meeting in February 2023. This included consideration of the purposes potentially served by biomarkers at different stages of drug development, and, alignment between biomarker measures and DSM diagnostic criteria for Major Depressive Disorder (MDD). GD further provided an overview of the current meeting (i.e., meeting 2) objectives, which were to explore further biomarkers to optimise the development of treatments for depression, and to then focus on industry needs in determining interest in forming academic-industry partnerships to evaluate and validate biomarkers of interest.

Caroline Golden (CG) highlighted the significance of examining primary symptoms individually to improve depression treatment efficacy – i.e. examining which symptoms precipitate other symptoms. GD and commented that the results of The PReDicT trial (sponsored by P1vital Products Limited; PPL) and other studies suggest antidepressants may have a greater impact on anxiety symptoms than depression, with potential subsequent improvement in depression.

Alastair Brown (AB) proposed stratifying patients based on symptom profiles to account for heterogeneity in depression. Speech analysis, including paralinguistic features, was discussed as a potential biomarker (used in e.g. RADAR-MDD), with particular relevance to psychomotor retardation.

Bridging preclinical and clinical biomarkers

Chair: Dennis Hernaus

Modelling affective bias in rodents - Emma Robinson

Emma Robinson (ER) discussed the limitations of both animal and human depression research in terms of mechanistic understanding. The benefits of objective measures were highlighted, as they enable the generation of translational models that relate human observations to animal research findings.

The effects of different drugs on learning were explored. Various bias tasks, such as the judgment bias task and affective bias test, were mentioned, and validity discussed. Conventional antidepressants were found to bias new learning in an amygdala-dependent way, while RAADs (rapid-acting antidepressants) such as ketamine seemed to bias retrieval, dependent on the prefrontal cortex.

The basis for a biomarker study comparing the mechanisms of conventional antidepressants and RAADs was discussed, focusing on affective biases and reward learning.

Findings of impaired reward-related learning in an early-life adversity model of depression and other pro-depression interventions in animals were described. Correlations between negative affective biases and reward learning deficits were observed. It was noted that, in general, inducing a negative affective state leads to negative affective biases.

Daniel Umbricht (DU) raised a question about measuring both positive and negative reward learning, as exist in schizophrenia. ER commented on challenges in getting animals to actively avoid punishment, and therefore some difficulties in measuring/leveraging negative reward learning were acknowledged.

The link between inflammation and depression was highlighted. Difference in SSRI response among MDD patients has been linked to inflammatory markers.

Reward and antidepressant drug action – Catherine Harmer

Cath Harmer (CH) outlined some performance outcome measures which can be used to measure reward processing in humans. The Probabilistic Instrumental Learning Task (PILT) was described - as a simple-to-use task with straightforward instructions, capable of being self-administered without the need for an experimenter. Use in the COSIE study was referenced as an example.

Both selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) have been associated with reduced punishment sensitivity. It was noted that neither drug led to an increase in sensitivity to wins compared to no treatment. A computational model suggested that these antidepressants reduce the potency of loss sensitivity rather than directly interfering with reward learning.

Pramipexole, as indicated by computational modelling, was found to reduce memory decay of reward and enhance learning about reward compared to a placebo. A bupropion study revealed a more complex picture, with a negative effect on performance observed at 2 weeks and then a rebound to healthy control levels by week 6.

An ongoing program at Oxford University focusing on ketamine, funded by the Medical Research Council (MRC) and Janssen, was mentioned. The RELAKS study included human analogues of tasks used in ER's animal experiments.

GD suggested using the COSIE data to identify a sensitivity-to-loss group, potentially not limited to individuals with depression, who might respond differently to certain antidepressant treatments.

The comparison of Pizzigali's Probabilistic reward learning task (PRT) with the tasks discussed in the meeting was brought up, and CH indicated that results from some of these reward processing tasks can be similar.

Fully leveraging the potential of mHealth using real-time analyses– Ulrich Ebner-Priemer

Ulrich Ebner-Priemer (UBP) gave an overview of approaches centred on passive monitoring and ecological momentary assessment (EMA), including considerations of burden. Compliance rates of up to 90% were observed in some studies, suggesting that the balance between data collection and burden was acceptable. The frequency and timing of participant alerts in data collection was discussed, including how triggering of prompts for data collection can be determined algorithmically. It was acknowledged that obtaining data over long periods, such as months or years, was challenging. Sensors (e.g. wearables, measuring physiology) are often not deemed suitable for longer-term use.

Concerns were raised regarding potential bias in data collection by focusing on data collection during extreme or interesting points in time or location. The response acknowledged the possibility of bias and explained that the aim was to capture rich data on rare events or according to specific triggers. The question of how to handle variations in data contribution among participants was also discussed.

Biomarkers - Current needs in industry

Chair: Andreas Reif

Best practices and the opportunity to identify sub-entities of MDD – Peter Schueler

Peter Schueler (PS) provided a presentation and discussion of patient registries, giving NESDA as an example of how registries can require significant initial investment but then attract funding and therefore offer good overall return. Registries were presented as not complicated to maintain, except for agreement on specific procedures/measured to be included in data capture. It was emphasized that sharing information with patients is important for empowerment and that registries are evolving into platforms resembling social media, fostering community building and facilitating learning and peer-support between individuals with similar experiences.

Data confidentiality and security were mentioned as important considerations. The concept of tokenization was discussed as a potential solution. Scandinavian cohorts were mentioned, highlighting the differences in healthcare systems compared to other regions, and use of tokenisation.

Issues were discussed regarding the usefulness of data in researching anhedonia, as self-report can be challenging due to limited understanding of the concept by individuals and some treating clinicians.

The risks and benefits of sharing data with patients were also discussed. While concerns were raised about patients making decisions based on their data, it was noted that in many cases, individuals want their data to be used to help them.

Regarding the timeframe for establishing registries, particularly in countries like Germany, it was acknowledged that gaining traction can be challenging. Pressure for progress is expected to come from the bottom-up as individuals desire their data to be utilized for their benefit.

Advancing novel therapeutic compounds for anhedonia: BI's perspective – Elizabeth Tunbridge

Elizabeth Tunbridge discussed the BI approach to drug development for symptoms of anhedonia, inspired by Research Domain Criteria (RDoC), and focusing on a transdiagnostic understanding of illness. It was acknowledged that current understanding in the area of anhedonia is limited, with animal models still quite crude and a lack of biomarkers and validated tests. The need for scalable and approved endpoints, as well as potential changes in the way healthcare was delivered, was mentioned.

The understanding of anhedonia in patient groups, such as depression vs. schizophrenia, was noted as still insufficient. It was suggested that as a consortium, a follow-up to RTOC (Reward Task Optimization Consortium) would be valuable, with the focus on early clinical change detection and the ability to link findings to circuit biology. The need for a biomarker that is sensitive at the individual level to demonstrate clinical efficacy was emphasized. The challenge of acceptability of such biomarkers to regulatory authorities was also highlighted, along with the importance of prognostic capabilities and their applicability in different cultural contexts (e.g., China, India, Europe).

The convening power of ECNP (European College of Neuropsychopharmacology) was acknowledged, and the idea of a white paper addressing regulatory issues was raised. The potential for ECNP to facilitate collaboration and the collation of transdiagnostic datasets for reverse translation was also discussed.

AR raised how roundtable on biomarker-directed therapy for MDD was to be held in Germany involving Biogen, Boehringer Ingelheim, and other organizations. The possibility of a further meeting in Nice, France in the spring of next year was also raised.

The importance of including non-pharmaceutical stakeholders, such as patient advocacy groups, in the discussion and initiatives was highlighted.

Specific discussions on differentiating anhedonia and the impact of antidepressant treatment on emotional blunting were mentioned. Some researchers such as Andrea Cipriani hold clinical trial datasets of different compounds, including scales such as MADRS (Montgomery-Åsberg Depression Rating Scale) which includes an item about experience of pleasure.

Precision psychiatry – vision, opportunities and challenges for the Pharmaceutical Industry – Tamara Werner-Kiechle

Tamara Werner-Kiechle described the opportunities and issues around precision psychiatry from an industry perspective. It was acknowledged that the power of biomarkers lies not only in patient identification but also, or mainly, in assessing treatment efficacy. Psychiatry was noted to be evolving at a slower pace compared to oncology and somatic medicine.

Challenges were mentioned in implementing ketamine treatment protocols, particularly the difficulty in getting healthcare professionals to adopt non-standard processes, such as having a dedicated chair in a special room. Aticaprant's potential to improve symptoms, specifically targeting anhedonia by reducing the suppression of dopamine and serotonin activity, was discussed.

Differences in the evidence for validity of scales including DARS, MADRS, and PHQ9 as measures for assessing anhedonia were discussed, as was the impact of cultural variations on patient-reported outcomes and clinician reported outcomes in relation to language and understanding.

AR highlighted the importance and challenges of depression advocacy groups, with a mention that they may sometimes be overshadowed by more instrumental groups, such as those advocating for ADHD, autism, or anti-psychiatry in schizophrenia. Difficulties in setting up collaborations between industry and patient advocacy groups in Europe, compared to North America, were mentioned. ECNP was acknowledged as a valuable platform for facilitating such partnerships.

Motivating Speed Dating - Alastair Brown

Alastair introduced the GPCR biotech, Sosei Heptares. The talk focused on the small company's perspective on addressing complex disorders like depression, with particular interest in anhedonia. The challenges for a small company of conducting Phase 2 trials without clear biomarkers for patient identification and establishing mechanisms were highlighted.

Collaboration with National Institute on Drug Abuse (NIDA) was mentioned, specifically in the context of anhedonia and substance abuse. The importance of defining new treatment areas and ensuring the continuation/establishment of care pathways was emphasized. The value of a transdiagnostic approach was acknowledged. Research gaps in anhedonia, substance abuse, and comorbidity with alcohol use disorder (AUD) were identified. There is limited research on prevalence and comparative research, as well as a lack of longitudinal studies. A proposal to create a database to address these objectives was mentioned.

Work looking at BEHAPP endpoints in the NESDA cohort (depression) were mentioned, as was a precompetitive study being conducted at King's College London (KCL) on treatment resistant depression (TRD) response to ketamine. Measures in the precompetitive study include EEG (e.g. neuroplasticity), scales such as QIDS (Quick Inventory of Depressive Symptomatology) and DARS (Dimensional Anhedonia Rating Scale), and fluid biomarkers. The study is expected to read out at the end of the year.

CG expressed appreciation for the mechanistic approach of RDoC but cautioned that a sole focus on RDoC might make it challenging to demonstrate clinical efficacy. The consensus was that precision psychiatry will not be achieved immediately, but there may be separate trials targeting anhedonia in depression and schizophrenia.

The dependence of smaller companies on large companies for R&D initiatives was acknowledged.

SESSION 2 – TUESDAY 27 JUNE 2023

Biomarkers - Current needs in industry

Chair: Andreas Reif

Key opportunities and challenges bringing RAADs to patients in Europe – Sean Knox and Aneta Skwarlinska

Biogen was introduced, highlighting its founders' expertise in genetics, neuroscience, and neuropsychiatry. The meeting discussed unmet needs within the scope of RAADs, focusing on the challenges faced in this area. Differences in Health Technology Assessment (HTA) approaches among European nations were addressed, with France (FR) and Germany (DE) emphasizing clinical outcomes and strict clinical trial design, whilst the UK has relative emphasis on health economic, and Spain / Eastern European countries emphasize budget impact due to budget constraints.

The importance of considering specific challenges in developing RAADs, such as identifying the best active comparators and designing studies with 6-month follow-up to demonstrate sustained efficacy, was discussed. It was noted that the focus on clinical and economic outcomes might overlook wider societal issues and impact related to RAADs.

The presentation outlined ways forward for RAADs, raising questions regarding characterizing unmet needs in patients with MDD, demonstrating benefit for patients, adapting clinical trial designs to reflect this benefit, exploring the potential role of biomarkers, and bridging the gap between clinical and economic perceptions.

The session explored the idea of constraining the definition of depression, acknowledging that much prescribing occurs for individuals with stress-related problems, fatigue, chronic fatigue, and burnout who may not strictly meet criteria for depression. The discussion highlighted the potential difficulty in demonstrating greater efficacy of RAADs compared to conventional antidepressants in this group. Stratifying patients and deconstructing the phenotype were suggested as approaches to address this challenge.

Tandem development of novel antidepressants and genetic companion diagnostics – Opportunities and challenges – Hans Eriksson

Hans' talk presented the HMNC Brain Health approach to utilizing genetic and other biomarkers, together with artificial intelligence (AI) as companion diagnostics. The study design for a placebo controlled clinical trial was described, involving pre-specified tests to stratify MDD participants as high, mid, and low in terms of underlying HPA-axis dysfunction. The expectation was that the high group would exhibit the greatest response to the compound, a vasopressin V1b receptor antagonist. The response of the other two groups remained unclear and was a point of interest in the study.

The discussion shifted to the clinical reality of using biomarker tests in practice as a companion diagnostic. For example, it was questioned whether it is realistic to expect doctors to run a test that takes 10 days to produce results, with a 33% chance of indicating a specific antidepressant. The idea of having a single test that points to specific antidepressants from an array was presented as an ideal scenario.

Questions were raised regarding the turnaround time for test results, the sensitivity and specificity of the test in predicting response to DEX/CRH (dexamethasone/corticotropin-releasing hormone), and the generalizability of the test results. In response, the emphasis was placed on generating new data at this stage.

The importance of getting the dose right – Torbjörn Waerner

The session focused on the importance as well as challenges of identifying the correct dose in drug development. Historical demonstrations of this were provided: e.g. Roche, where a drug may have had an incorrect dose initially (too low), requiring further data collection and analysis. An antipsychotic launch at Lilly was discussed, where the initial recommended dose of 10mg was revised to 20mg based on additional data collection. Side effects such as diabetes and obesity were described.

Regarding antidepressants, it was noted that doctors sometimes observe a response in less than 3-4 weeks, while in other cases, no effect is seen and the dose is increased after a few weeks. Concerns were raised about patient disappointment, healthcare burden, and onward patient impact.

Reflections were shared on dosing issues in the development of vortioxetine, including negative US studies leading to higher dosing recommendations. Corrupt sites, investigators, and patients participating in multiple clinical trials without drug presence in serum in US studies were discussed.

The “peak experience” in psychedelic therapy, described as an ineffable experience, was discussed. Three domains from the peak experience were identified as potential markers of efficacy: intensity, profoundness, and loss of control. Questions were raised about the necessity of the peak experience and the potential efficacy of non-psychedelic psychedelics and low doses. AR described a case study involving a patient treated with psychedelics, who reported no peak experience but still experienced a robust antidepressant effect. It was noted that the patient had been taking trazodone, a 5H2A blocker, which raised questions about the necessity as well as pharmacology of peak experiences.

Variation in the quality of psychedelic experiences was acknowledged. It was suggested that self-report may not be the best assessment method.

The meeting explored the interest in combining new treatments with cognitive-behavioral therapy (CBT) and the potential for restructuring “anhedonic circuits” through neuroplasticity.

CONCLUDING DISCUSSION:

GD presented a summary of the main themes arising from the current meeting, and provided a framework of three main "work packages" where there was overlap between parties in terms of interest, need, and perceived opportunity. These were seen as representing areas of potential collaboration and were discussed at length in the closing Discussion session.

Elizabeth Tunbridge (ET) shared information about an IHI call (new IMI) and invited participation from pharmaceutical and tech companies. Trial-ready cohorts were mentioned as one possibility already being discussed at the conception stage of the call.

A separate funding application was discussed, led by the University of Cardiff and MRC, which also aligned with the trial-ready cohort concept. The proposal emphasized early availability of cohorts and phenotyping, focusing on chronic depression and TRD. The potential for transdiagnostic approaches was also mentioned.

GD noted that recruiting individuals with depression and following them over time would eventually identify those with TRD, provided adequate longitudinal data is collected. DU acknowledged the importance of understanding the biology underlying depression but highlighted that it may not be as directly relevant to drug development as measuring efficacy. In discussion, a response was articulated that emphasized the need to tackling heterogeneity in response, and how underlying biology may determine this.

The challenges and importance of characterizing and measuring anhedonia in drug development were discussed, including the lack of awareness among healthcare professionals. TW mentioned interest in studying individuals who fully recover from depression.

The potential of genetic biomarkers was addressed, with reference HRCM's approach and their search for scalable correlates of treatment response, particularly related to specific single nucleotide polymorphisms (SNPs) associated with vasopressin function. Data-driven approaches in identifying genetic associations with TRD were also mentioned.

Attendees shared their perspectives on the clinical trajectory and heterogeneity of patients with MDD. The idea of describing patient heterogeneity and what can be achieved in understanding and treating the condition was further discussed.

At the conclusion of the study a summary of work projects arising from the discussion, and leads, was agreed:

WP	THEME	LEADS
WP1	Patient Cohorts	Peter Schueler, Gerry Dawson

WP2	Depression subtypes; anhedonia	Liz Tunbridge, Tamara Werner-Kiechle, Dennis Hernaus
WP3	Dissemination	Alex Schubert, Martien Kas, Andreas Rief