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INFORMATION BULLETIN ISSUED AS A SERVICE TO THE MEDICAL PROFESSION

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THE INFLUENCE OF OBJECTIVELY COLLECTED MEDICATION ADHERENCE INFORMATION ON TREATMENT DECISIONS FOR BIPOLAR I AND MAJOR DEPRESSIVE DISORDER: A RANDOMIZED CASE VIGNETTE STUDY

Introduction:

Serious mental illnesses, such as bipolar disorder and major depressive disorder, are common and debilitating, as well as expensive to treat. Despite a wide range of effective therapies, these diseases are frequently difficult to treat. Symptoms frequently persist after the start of therapy, and relapse is common even after an initial response to treatment. The most effective decision, however, is determined by the reason for the non-response. A significant challenge is distinguishing between treatment non-response caused by an ineffective therapeutic and medication non-adherence. [1] It is critical to assess patient adherence accurately and on time. During the clinical interview, the most common approach is to ask the patient about medication adherence. Recent technological advances in monitoring patient adherence via digital systems, including ingestible and wearable sensors, can provide clinicians with accurate adherence information. [2] The study hypothesised that clinician decisions about treatment regimen modifications would differ depending on whether adherence data was objective or self-reported.

Methods:

A cross-sectional, random assignment survey of psychiatric clinicians who prescribe medication for the treatment of BD and/or MDD was conducted for this study. Clinicians (N = 180) were recruited using national association lists and given BD or MDD case vignettes that described symptoms, level of functioning, and self-reported medication adherence. Cases were assigned at random to vignettes that presented either subjective (self-report) or objective (refill rates and MEMS caps data) adherence information. Respondents were asked to make suggestions for changes to their medication regimen.

Results:

A total of 180 clinicians took part in the study. Participants in the BD arm (N = 90) were mostly female (55.5%) and specialised in psychiatry (97.8%). Participants in the MDD arm (N = 90) were

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mostly female (64.4%) and specialised in psychiatry (98.9 %). The BD arm was more likely to change antipsychotic treatment than mood stabilisers, while the MDD arm was more likely to change antidepressant treatment than antipsychotic prescriptions. Among non-adherence vignettes, cases that reviewed objective adherence data were more likely to use medication adherence enhancing interventions such as long-acting injectable antipsychotics. As expected, the rate of LAI selection was higher in cases reviewing BD vignettes than in cases reviewing MDD vignettes.

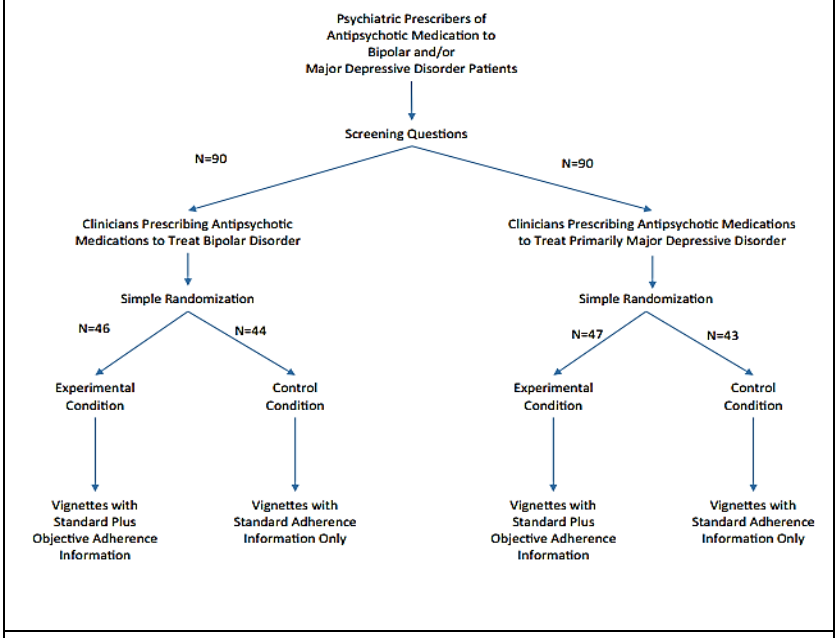

Fig 1. Randomization design

Discussion:

It may be necessary to provide clinicians with novel tools for accurately assessing adherence, allowing them to make more informed medication management decisions. Tools that assess adherence more accurately would reduce the frequency of poor outcomes such as unnecessary increases in medication dosage, prescription switching or prescription of adjunctive therapies, re-hospitalizations, labelling as "treatment resistant," and disruption of the recovery process, all of which are associated with the high cost of treating patients with BD and MDD.

Interestingly, if most clinicians believed (or were biased to believe) that their patients were non-adherent, objective adherence data would have had a greater impact on clinical decisions made in response to adherent non-responsive patients. These findings are consistent with data indicating the inherent difficulties in distinguishing between non-responsive and non-adherent patients, which may contribute to prescribers overestimating patient adherence to psychiatric medications. [3] These findings suggest that objective adherence data is most useful when treating BD and, to a lesser extent, MDD patients with antipsychotic medication whose symptoms are not well controlled, as it allows clinicians to distinguish between non-adherence and non-response to medication regimen.

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Fig. 2. (A–F) Bipolar disorder medication responses.

Conclusion:

This randomised trial discovered that having access to objective adherence data influenced clinician prescribing decisions when objective information indicating that the patient was non-adherent to their medication was presented. In the non-adherent cases, a greater proportion of controls assumed the patients were, whereas experimental group prescribers were aware of the patients' non-adherence. Though not as clearly defined as in the case of clinicians treating schizophrenia, there is a tendency to provide care that is more closely matched to the primary cause of poor symptom control: non-responsiveness or non-adherence to medication.

These findings suggest that the presence of objective adherence data may aid clinicians in distinguishing between medication nonresponse and medication nonadherence, as evidenced by the relationship between the presence of objective adherence data and treatment modification selection.

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A PILOT STUDY OF THE INFLUENCE OF BRIGHT LIGHT THERAPY ON ELECTROENCEPHALOGRAM-VIGILANCE IN THE TREATMENT OF DEPRESSION IN ADOLESCENTS

Introduction:

Depression is a major health issue that occurs at an increasing rate during adolescence. Despite extensive research on cognitive-behavioural approaches and medication, treatment outcomes for depressed adolescents remain unsatisfactory. As a result, better treatment is required. Bright light therapy (BLT), for example, is a non-invasive treatment with almost no side effects. [1] However, most treatment responses are based on self-reports, which may be biased and lack elucidated neurobiological changes that are associated with treatment response. As a result, there has been a call for more objective markers to estimate treatment responses, such as EEG biomarkers [2] As a result, the concept of vigilance may be useful: several studies show that adult depressive patients have higher arousal and a later decline during a resting state EEG-session than healthy controls, as well as a more stable vigilance regulation pattern than healthy controls. Vigilance is directly related to the negatively biassed and increased default mode network (DMN) activity in depression, which manifests itself as rumination, resulting in increased brain arousal, which may be altered by BLT.

Methods:

11 adolescents with depression who received BLT were compared to 11 age and gender-matched patients with depression who received standard treatment (TAU). For two weeks, the BLT was given in the morning on five consecutive days per week. The Beck Depression Inventory (BDI-II) was used to assess depressive symptomatology, and a 20-minute resting state electroencephalogram (EEG) was recorded. Before and after 10 days of treatment, EEG and BDI-II were measured. The VIGALL toolbox was used to calculate vigilance level and decline.

Results:

In adolescents with depression, brain arousal increased after 10 days of bright light therapy. Severe depressive symptoms were associated with higher levels of brain arousal; the BDI-II sum score correlated negatively with drowsiness.

Discussion:

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After 10 days of BLT, we found a statistically significant increase in vigilance in depressed adolescent patients. The TAU group also showed an increase in EEG vigilance, albeit to a lesser extent and without statistical significance. This increased vigilance after BLT, however, was not associated with a change in the BDI-II sum score or with the BDI-II sum score at baseline. This finding suggests that BLT may have an additional and immediate effect on vigilance that is not related to increased brain arousal in depression with symptoms such as inner tension or prolonged sleep latency. Instead, these findings are consistent with the reported improvement in sustained attention and sleepiness in sleep-deprived young adults following BLT. [3]

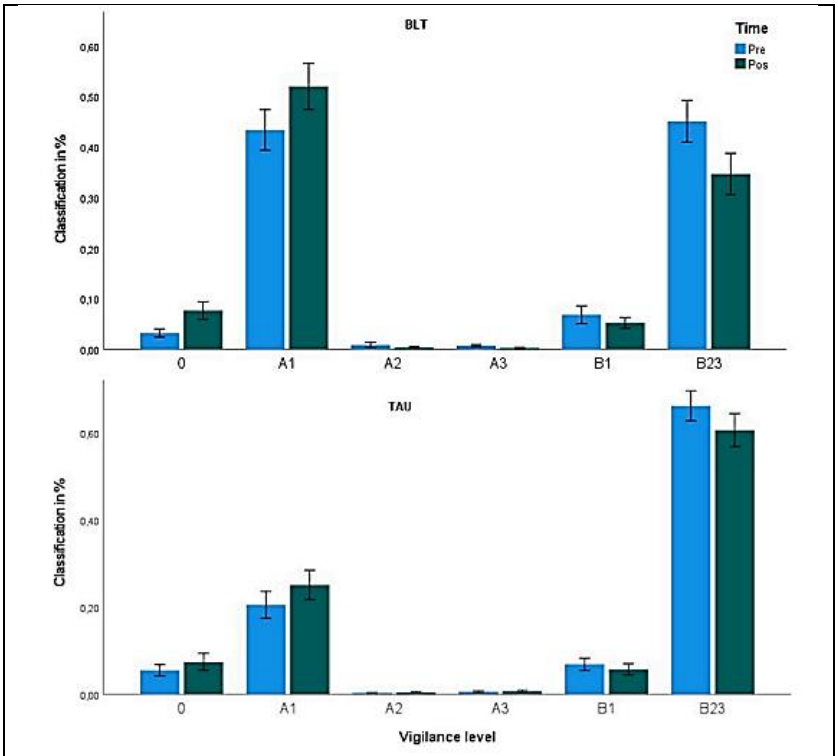

Fig.1 Vigilance classification distribution. BLT, Bright Light Therapy; shown are the mean percentage of vigilance level classifications. The 20 min resting-state EEG was second-wise classified by the VIGALL algorithm.

The normalisation effect of antidepressant intervention on increased brain arousal and EEG-vigilance in adult depressive patients was not observed, which could be attributed to the short time interval of only 2 weeks between baseline and follow-up. BLT side effects are likely to appear later in the treatment timeline. Nonetheless, the study discovered a positive correlation between the BDI-II sum score and the B23 vigilance level, indicating that severe depressive symptoms are associated with higher levels of brain arousal, as previously described for adults. [4]

Conclusion:

The markers chosen proved to be reliable and valid predictors of neurobiological changes associated with depression and its treatment. To replicate the presented results, larger sample sizes and longer follow-up times will be required in future studies.

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The BLT may also have an effect on brain arousal. EEG vigilance appears to be a reliable and valid marker for neurobiological changes associated with depression and its treatment, and thus may be clinically relevant.

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A NEW APPROACH TO DETECT FUNCTIONAL CONNECTIVITY PATTERNS ASSOCIATED WITH POSTTRAUMATIC STRESS DISORDER

Introduction:

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that significantly impairs social and occupational functioning. When people witness actual or threatened death, serious injury, or sexual violation, they may develop PTSD. Recent advances in fMRI analytic methodology have enabled a more comprehensive assessment of brain network interactions in neuroimaging research. According to the neurovascular coupling hypothesis, increased neuronal activity increases regional cerebral blood flow, which increases the fMRI signal known as blood oxygen level dependency (BOLD). [1] According to the triple network model, disruptions in connectivity of three key networks play important roles in many psychiatric disorders, including PTSD. The Salience Network (SN), Default Mode Network (DMN), and Central Executive Network (CEN) are linked to PTSD-related processes like extinction learning, autonomic and emotional regulation, conflict monitoring, and reward processing. SN and CEN showed increased connectivity, whereas DMN showed mixed results (increased vs. decreased). [2] The study proposes a novel analytic approach that combines graph theory and scaled sub-profile modelling (SSM), respectively, to identify degree centrality and dominant group-discriminating topographical patterns. The study proposes a novel analytic approach that combines graph theory and scaled sub-profile modelling (SSM), respectively, to identify degree centrality and dominant group-discriminating topographical patterns.

Methods:

This study compared group differences in resting state fMRI-based intrinsic connectivity in known resting state networks (RSNs) and graph theory-based measures between 11 patients with PTSD (PTSD-A) and 11 trauma-exposed controls (TEC). These 22 subjects were used in a combined analytic approach combining graph theory and SSM, which has the potential to identify more useful biomarkers than either alone. The study's performance was then tested in a new cohort (n =33) of 22 participants (PTSD-B) and 11 age-matched trauma-naive healthy controls (TNC) scanned with a different MRI scanner. These 33 subjects were from an ongoing study at a different research centre, so the acquisition parameters were different.

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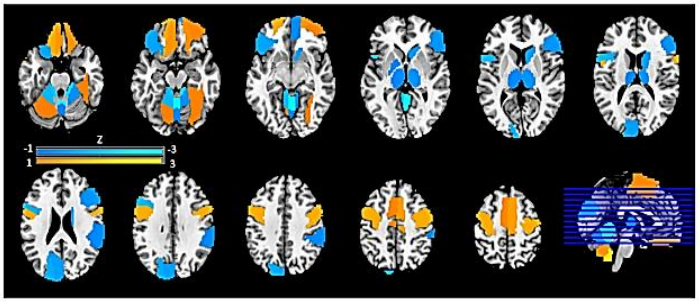
Results:

There were no significant group differences in intrinsic connectivity of known resting state networks or graph theory metrics (clustering coefficients, characteristic path length, small worldness, global and local efficiencies, and degree centrality). The graph theory/SSM analysis revealed a topographical pattern of varying degree centrality that distinguished PTSD-A from TEC. This PTSD-related network pattern expression was also studied in a separate cohort of 33 subjects scanned with a different MRI scanner (22 patients with PTSD or PTSD-B and 11 healthy trauma-naive controls or TNC). Pattern expression scores were significantly lower in the TEC group across all participant groups, while PTSD-A, PTSD-B, and TNC subject profiles did not differ.

Discussion:

For cohort A, maximizing the differences between the two groups (PTSD-A vs. TEC) was critical for the study's SSM prediction model to identify the group differentiating pattern as principal components with non-negligible covariance (>5%), and thus stricter diagnostic criteria without overlap between the two groups (CAPS-IV 45 vs. CAPS-IV 30) were applied. The study's goals for cohort B, on the other hand, were to see if the proposed PTSD-related function connectivity pattern has clinical relevance (i.e, correlation with symptom severity in PTSD-B) and to see if the pattern expression developed in response to trauma exposure. As a result, the PTSD-B group had a broader range of PTSD symptom severity, and four of the 22 patients did not meet the CAPS-5 diagnostic threshold.



Topographical distribution of PTSD-related functional connectivity pattern. SSM analysis18 was conducted to the degree centrality matrix of subject × ROIs to identify principal components. Stepwise regression analysis was performed to define a group discriminating pattern resulted in a linear combination of fourth and sixth principal components, accounting for 13.8% of total covariance

While TNC subject profiles did not differ significantly from either PTSD group, TEC showed significantly lower expression of the pattern when compared to all other groups (PTSD-A, PTSD-B, and TNC). Unlike what we expected, regions like the amygdala, hippocampus, insula, and cingulate cortices were not crucial to our network configuration. One interpretation is that the inverse of our degree centrality pattern, which is more prominent in TEC than in PTSD or TNC, may represent

compensatory mechanisms resulting from trauma exposure and the development of PTSD. If this is the case, it is possible that the regions traditionally associated with PTSD pathophysiology are not necessarily the most important here. Rather, subcortical structures, occipital and cerebellar cortices, which have modulatory functions on limbic structures as well as sensory and emotional processing, were identified as significant in the study's pattern. [3]

The intrinsic connectivity in the visual medial network was significantly higher in TEC subjects. In comparison to previous studies, the lack of significant difference in any node from the triple network model is not surprising. Another study, for example, discovered high salience network intrinsic connectivity (referred to as global brain connectivity in the paper) in asymptomatic combat controls. However, this was only observed during task-based fMRI; resting state investigations revealed no differences in salience network intrinsic connectivity between groups. They also discovered no difference in CEN connectivity between resting groups.

Conclusion:

The combined approach of graph theory analysis and scaled subprofile modelling has been successfully used to determine neurological disorders and aid in diagnosis. The researchers present its utility in characterising psychiatric disorders such as PTSD in this paper. Future research into this approach, with a larger sample size, could pave the way for the development of neuroimaging biomarkers for psychiatric symptoms and disorders.

In the PTSD-B group, the pattern's expression level was related to symptom severity. This method has the potential to develop objective biomarkers for PTSD. There will be a discussion of possible interpretations and clinical implications.

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CLINICAL ASSESSMENT AND MANAGEMENT OF A 45-YEAR-OLD MAN WITH CONFUSION, PSYCHOSIS, AGITATION, STEREOTYPED BEHAVIOR, AND IMPAIRED SPEECH

Introduction:

Since chlorpromazine was first used effectively to treat psychotic symptoms in the early 1950s, psychiatric medicine has made significant progress in managing complex psychotic and behavioural symptoms. Psychiatrists have also gained more scientific knowledge that allows them to link patients' clinical symptoms to dysfunctional brain systems. Managing brain neurodegeneration and its associated psychotic and behavioural symptoms, on the other hand, remains a challenge for psychiatrists today. [1] Many basic and clinical scientists are interested in researching brain neurodegeneration. It is well understood that brain neurodegeneration can occur quickly or gradually. Clinically, psychiatrists must assess patients' cognition and intervene on reversible causes of brain neurodegeneration. Chronic alcohol use has been shown to cause brain neurodegeneration due to alcohol neurotoxicity. Furthermore, alcohol use can result in Wernicke's encephalopathy and Korsakoff syndrome. Each of these two conditions has a unique and complicated clinical presentation. [2] Clinically, recognising a patient's cognitive deficits may be simple; however, understanding the underlying aetiology is frequently more difficult. Patients suffering from chronic mental illnesses frequently have comorbidities such as addiction, physical disability, and malnutrition, all of which can contribute to their physical and mental decline. Treatment can be difficult as their clinical pictures become more complicated.

Case Report:

Mr. A, the 45-year-old patient, is mentally and physically disabled. As a teenager, he was diagnosed with bipolar disorder. He suffered a lumbar spinal injury in his twenties as a result of a car accident, which caused weakness, numbness, and frequent infection in both of his lower extremities. Over the course of his life, he also became addicted to alcohol. Mr. A arrived at the facility with severe neuropsychiatric symptoms. Doctors were able to control his symptoms of agitation, self-harm, mood swings, and stereotyped behaviour by employing a variety of clinical strategies. However, the doctors were unable to improve his neurocognitive functioning or speech impairment, which appeared to worsen and become irreversible in a matter of months.

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The mixed treatment responses left doctors disappointed and perplexed. Several laboratory tests and imaging studies were performed to better understand Mr. A's clinical presentation. To manage his symptoms, he was given a variety of psychotropic medications. Gradually, the doctors felt that we were gaining a better clinical and etiological understanding of this case. His bipolar disorder, alcohol addiction, and physical injury had all likely contributed, either directly or indirectly, to his neuropsychiatric symptoms. It is very likely that his alcohol-related progressive dementia, in addition to his chronic bipolar disorder, aided in the progression of his brain neurodegeneration. Furthermore, Wernicke-Korsakoff syndrome could be considered to have developed during his clinical course. Furthermore, the fluctuation of the patient's neuropsychiatric symptoms observed during his hospitalisation reflects the human brain's increased vulnerability to sustained neurodegeneration.

Discussion:

Following the completion of these extensive studies, psychiatry appeared to be the best explanation for Mr. A's complicated symptoms. His long history of heavy alcohol consumption, chronic bipolar disorder, and poor self-care were all taken into account. Mr. A's brain neurodegeneration was likely caused by a combination of factors, including progressive alcohol-induced dementia, ongoing bipolar disorder episodes, repeated infections, and metabolic encephalopathy. Wernicke-Korsakoff syndrome is another possibility for Mr. A's suspected brain neurodegeneration.

Mr. A's BMI was 19.5, which was within the normal range, but he had been reliant on "junk food" for years due to difficulty ambulating and poor self-care. Malnutrition was suspected in Mr. A's case and can be an exacerbating factor for Wernicke-Korsakoff syndrome, as malnutrition can cause Wernicke-Korsakoff syndrome on its own. [3]

Mr. A did not receive a formal ophthalmological examination during his hospitalizations. There was no evidence of abnormal eye movements such as ophthalmoplegia, nystagmus, anisocoria, or outward gaze palsy. Although Wernicke encephalopathy is a pathologically progressive disease, clinically, Korsakoff syndrome is thought to be irreversible. [4]

After patients have passed the acute stage of Wernicke syndrome, bolus IV thiamine infusion is generally regarded as ineffective. This could account for Mr. A's failure to improve after his IV thiamine infusion. Furthermore, Korsakoff syndrome may be caused not only by thiamine deficiency

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but also by deficiencies in other nutrients or by alcohol-induced neurotoxicity. Mr. A's brain MRI revealed no evidence of neuronal degeneration in the mammillary bodies, a common neuropathology in Wernicke-Korsakoff syndrome patients. His MRI, on the other hand, revealed some nonspecific brain abnormalities in the periventricular white matter of both cerebral hemispheres. Another brain region reportedly affected by Korsakoff syndrome is the periventricular area. [5]

Conclusion:

In conclusion, Mr. A's clinical presentation and course highlight a complicated and one-of-a-kind case. We can conclude from this and other reported cases that patients with chronic mental illnesses are more likely to have comorbid addiction and physical illnesses. These patients are especially susceptible to neurocognitive decline. Clinicians must be prepared to address and treat all aspects of the care of these patients.

The fluctuation of the patient's neuropsychiatric symptoms observed during his hospitalisation reflects the human brain's increased vulnerability to sustained neurodegeneration.

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