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Neurocognitive impairment among incarcerated HIV positive people

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Introduction: Neurocognitive impairment poses a multifaceted challenge among individuals incarcerated while living with HIV, reflecting the interplay of medical, social, and systemic factors within carceral settings. In these environments, where stress, trauma, and limited access to healthcare prevail, the prevalence and severity of neurocognitive impairment among HIV-positive inmates are notably elevated.

The purpose of this study was to evaluate the cognitive impairment of HIV-infected individuals in penitentiary institutions in Azerbaijan and its relationship with various indicators.

Methods:A cross-sectional methodology was employed to enroll incarcerated individuals diagnosed with HIV from prisons in Azerbaijan. Approval for the study was obtained from the Ethics Committee of Azerbaijan Medical University (Reference: P.23/19.05.2022). Prior to participation, all individuals provided written informed consent after receiving comprehensive information about the study.

Data regarding demographic and clinical characteristics were collected as part of the study protocol. HIV-associated neurocognitive disorders (HAND), were defined by the Frascati criteria and were categorized into asymptomatic neurocognitive disorder (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). Additionally, the anxiety and depression levels of patients were assessed using the Hospital Anxiety and Depression Scale (HADS).

Quantitative and qualitative data were analyzed using medical statistical methods. Statistical significance was set at $p < 0.05$ for hypothesis testing.

Results:A total of 140 HIV-positive patients incarcerated in Azerbaijan were examined, with a median age of 43 years (range: 23–62). Among them, 132 (94.3%) were male, and 8 (5.7%) were female. The median cells (cluster of differentiation 4) count was 447 cells/μL (range: 41–1291). A majority of patients (50.7%) had been HIV-positive for more than 5 years. Comorbid depression was observed in 48 (62.9%) patients, while 47 (62.1%) exhibited varying levels of anxiety.

Regarding neurocognitive disorders (HAND) among the prisoners, asymptomatic neurocognitive impairment (ANI) was identified in 43 (30.7%) patients, mild neurocognitive disorder (MND) in 74 (52.9%), and HIV-associated dementia (HAD) in 23 (16.4%). HAND was more prevalent (69.6%) among patients receiving antiretroviral therapy (ART) for less than 5 years.

Conclusions: This study highlights the importance of comprehensive care approaches that integrate HIV management, mental health support, and strategies to mitigate the stressors associated with incarceration. Addressing neurocognitive impairment among incarcerated individuals living with HIV should not only aim to improve the quality of life for this vulnerable population, but also seek to enhance public health outcomes and promote social justice within our communities.

Keywords: HIV, prisoners, neurocognitive disorder, dementia

A Multidisciplinary Approach to Preventing Postoperative Delirium in Older Adults: The PROTECT Trial.

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Background and objectives: Delayed neurocognitive recovery (dNCR) after anaesthesia and surgery is common in older adults. For many people dNCR precipitates long-term cognitive impairment, functional decline or dementia. Such adverse outcomes are often proceeded by avoidable complications such as postoperative delirium (POD). Rather than pharmacological interventions, the most effective way to prevent POD and subsequent long-term neurocognitive disorders is with behavioural interventions. In the PROTECT trial, we aim to reduce the incidence of POD and associated cognitive decline, in older people undergoing elective surgery, by implementing a multidisciplinary perioperative intervention.

Method: In this prospective, single-blinded, pragmatic, randomised trial we will compare a tailored multidisciplinary perioperative pathway against current standard of care practices. We have recruited 119 (from a target of 692) elective surgical patients aged over 65 and randomised them in a 1:1 design. Our perioperative intervention targets delirium risk reduction strategies by emphasising the importance of early mobilisation, nutrition, cognitive orientation, sensory aids and avoiding polypharmacy. To promote healthy behaviour change, we provide all intervention participants with a tailored psychoeducation program both preoperatively (prehabilitation) and postoperatively (rehabilitation), focusing on cardiovascular and psychosocial risks for cognitive and functional decline.

Results: To assess the efficacy of our intervention we perform neuropsychological test batteries at: baseline, three, and 12 months postoperatively. We will monitor delirium daily through the patient's admission using the 3-minute Confusion Assessment Method (3D-CAM) or, if appropriate, an adapted version for the intensive care unit (CAM-ICU).

Conclusions: Delirium is a common and debilitating postoperative complication that contributes to the cognitive and functional decline of older adults. By adopting a multidisciplinary, behavioural approach to prevention, we aim to reduce the social and economic burden of delirium and by extension cognitive decline in older Australians.

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Cognitive impairment in type 2 diabetes: A study in Tbilisi, Georgia

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Introduction: Cognitive impairment among people with Type 2 Diabetes Mellitus is a great challenge in everyday clinical practice. Cognitive impairment significantly affects the quality of life and self-care and independent living. This small study was carried out to evaluate the prevalence of cognitive impairment among patients with Type 2 Diabetes Mellitus (T2DM).

Methods: We assessed cognitive function in type 2 diabetes patients compared with controls without diabetes, using Addenbrooke's Cognitive Examination-III (ACE-III) test. Age, gender, comorbidities, education, and HbA1C were correlated with the test results.

Results: 42 patients with Type 2 Diabetes Mellitus and 45 controls were enrolled in the study. The mean age was 62.5 ± 6.2 for T2DM group and 61.8± 6.1 for controls. The mean HbA1c was 8.8 ± 2.5% in T2DM group. Cognitive impairment was more prevalent among type 2 diabetes participants (Odds ratio 33.1, CI: 10–100, $P < 0.0001$) with mean Addenbrooke's score of 70.9 ± 11.1 compared to 86.9 ± 5.3 in controls ($P < 0.0001$). The adjusted Odds ratio for CI was 9.46 after adjustment for hypertension, 9.12 after adjustment for dyslipidemia, 7.18 for age. People with diabetes of higher age groups scored significantly lower than the control of higher age groups ($p<0.05$). There was a statistically significant association between cognitive scores and dyslipidemia in patients with diabetes and controls (82 ±2.03 in patients with diabetes group with dyslipidemia versus 92.50 ± 2.09 in the control group with dyslipidemia, $p<0.05$). Undergraduate controls scored higher than patients with diabetes undergraduates, $p < 0.05$. The correlation with gender as well as HbA1c was not significant ($p>0.05$).

Conclusions: Diabetes is associated with a decline in cognitive function. Addenbrooke's cognitive assessment (ACE-III) is a useful tool to detect cognitive impairment in patients with Type 2 Diabetes Mellitus. Future comprehensive studies are needed to optimize diagnostic and preventive measures of cognitive impairment among those with Diabetes.

Geriatric Depression Scale Correlation with Pain in Georgian Perioperative Elderly Patients

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Introduction: According to the National Statistics Service of Georgia, individuals aged 65 and over currently constitute 15% of the country's population (1). We investigated the incidence of perioperative depression and its correlation with pain levels in a Georgian geriatric surgical population who underwent major elective orthopedic surgeries,comprizing total hip and knee joint replacements.

Methods:Participants included those who were cognitively fit, based on a Montreal Cognitive Assessment (MoCA) test with a score of 22 or more. The participants, aged 65–80 years, included 81% women, 22% still working, 73% classified as ASA II, and 27% as ASA III. The Geriatric Depression Scale (GDS) and Numerical Rating Scale (NRS) for pain were administered preoperatively, on the day of discharge, and at 1 month and 3 months postoperatively. Additionally, NRS was administered twice daily (morning and evening) during the hospital stay.

Exclusion criteria included dementia, surgery within the last six months, or inability to complete assessments. All participants provided written informed consent. Statistical analysis was conducted using SPSS.

Results:We present pilot results from the first 150 individuals. We evaluated the prevalence of depression in our participants at each of the specified time points. Preoperatively, (29) 19% of patients reported depression. This increased to (34) 23% at discharge, (60) 40% one month postoperatively, and decreased slightly to (38) 29% three months postoperatively. These results indicate a rise in the rate of depression, indicative of an increase in incident depression during the postoperative period.

We also assessed average pain levels for the same patients at each time point using the NRS which has a range of 0 – 10, with 0 being no pain and 10 being severe pain. Baseline pain was reported as mean (SD) 7.6 (1,4). Postoperative pain averaged 4.7 (0,1), pain one month postoperatively was 2.6 (1,3), and pain three months postoperatively was 0.9 (1,1).

Lastly, we examined the correlation between GDS scores and pain levels. Regression analysis revealed a positive correlation between GDS and pain, with the strongest correlation observed between pain at one month and GDS at one month ($\beta = 0.67$, 95% CI: 0.31, 1.02, $p < 0.01$) and three months ($\beta = 0.77$, 95% CI: 0.32, 1.23, $p<0.01$.

Conclusions:The findings of this preliminary analysis demonstrate an association between increasing depression scores and increasing pain in the postoperative period following elective joint replacement surgery. Future research should investigate the direction of this association and consider mitigation strategies for both depressive symptoms and postoperative pain.

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1. https://www.geostat.ge/ka/modules/categories/41/mosakhleoba

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Frailty, decline across organ systems leading to increased susceptibility to stressors[1], and delirium, an acute attentional deficit[2], are examples of geriatric syndromes. Geriatric syndrome is a prevalent and multifactorial condition that preferentially impacts older adults[3]. Geriatric syndromes are a different concept than disease; for the latter the etiology, pathogenesis, and symptoms are all known. In contrast, geriatric syndromes have multiple etiologies, interacting pathophysiology, leading to a unified manifestation.[3] This framework provides insight regarding why we have found many ways to identify frailty[4] and delirium[5], but that treatment remains elusive. It is likely that patients may manifest frailty or delirium due to a diverse group of pathophysiologic reasons. For example, a recent epidemiologic study found that there are different delirium risk factor "phenotypes" for endarterectomy, general surgery, and orthopedic surgery patients[6]. For example, the endarterectomy group had health and cognitive risk factors, while the orthopedic surgery group had risk factors predominantly related to pain. One could extrapolate that the pathophysiology leading to delirium may also differ by risk factor group, a direction for future research. The geriatric syndrome paradigm also explains why frailty is strongly associated with delirium (more than twice the risk) across studies[7] but not specific for delirium[8]. The underlying pathophysiology of frail patients may differ and may combine with other factors (or not) to cause delirium. Novel approaches to understand the overlap between frailty and delirium using proteomic technology have uncovered a wide range of pathways[9,10]. For example, proteomic signatures are associated with inflammatory processes and vascular system function, such as angiogenesis[11]. For example, a recent study found a proteomic frailty signature that can predict the development of frailty up to ten years prior to clinical diagnosis[12]. A systems biology approach can then be applied to these signatures to identify which pathways may connect frailty and delirium. This type of work will provide opportunities to target specific pathology and holds promise for the development of more specific interventions.

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Wearable devices (actigraphy) to monitor sleep and exercise and inform delirium prevention strategies

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Perioperative Neurocognitive Disorders (PND) including postoperative delirium (POD) and postoperative neurocognitive disorders (postoperative NCD) are the most common complication following anaesthesia and surgery for patients aged 65y or more. These complications are associated with a significant increase in morbidity, mortality, risk of dementia and risk of institutionalization. The highest risk of these poor outcomes follows the occurrence of POD which occurs in up to 52% of patients, depending on type of surgery, frequency of assessment and the type of assessment.

It is widely acknowledged that up to 30 – 40% of delirium is potentially preventable, yet the interventions are resource intensive and therefore have not become part of routine practice. Having the ability to identify those at risk would aid intervention strategies by enabling the sub-set of at-risk individuals to be targeted for interventions to prevent or reduce the incidence and severity of POD.

The investigation of wearable devices to diagnose or detect a medical condition has been increasing over the past two decades, with an exponential increase in recent years in parallel with advances in technology. Wearable devices have been shown to be effective for monitoring of disease (e.g. Parkinsonian tremors) and for detecting disease (e.g. cardiovascular disease), as well as monitoring sleep, activity (actigraphy) and physiological parameters.

Actigraphy has been used to detect physiological and sleep differences in patients with and without delirium, as well as offering the ability to determine the subtype of delirium. The ability to accurately measure sleep remains difficult in routine clinical care of surgical patients, yet an association between poor sleep quality and quantity is associated with an increased risk of POD. The use of electroencephalography (EEG) in combination with actigraphy has the potential to identify patients at high-risk of POD and further cognitive and functional decline. This would provide a window to administer preventive interventions, both pharmacological and non-pharmacological, to prevent POD and other PNDs to improve recovery and potential complications for older adults undergoing anesthesia and surgery.

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The neurofeedback therapy effect on impulse control and sustained attention in children with ADHD

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Introduction: According to the ICD-11 and DSM-5 criteria, Attention Deficit Hyperactivity Disorder (ADHD) is classified as a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity. Neurofeedback therapy is a common treatment option for ADHD; however, there remains debate regarding whether behavioral improvements result directly from the training method. The Infralow Frequency (IL-F) individually tailored training protocol has demonstrated an increase in sustained attention and impulse control in children with ADHD.

Methods:13 children diagnosed with ADHD, aged 8–13, participated in the study after obtaining informed consent. Electrode placement and training frequency were selected based on guidelines for symptom tracking, neuropsychological diagnostics, and QIK-Test results. Data were analyzed using the SPSS program.

Results: Intermediate QIK-Test results after 10–12 IL-F training sessions revealed improvements in sustained attention and impulse control compared to baseline measurements. Baseline sustained attention was reported as mean (SD) 51.23(43.20). After electrode placement and training 81.08 (27.68). Baseline Impulse Control was reported as mean (SD) 62.77 (46.17). After electrode placement and training- 91.85 (16.94). Because data didn't have normal distribution, nonparametric Related Samples Friedman's Two-Way analysis of Variance Test was used. Comparing Baseline Sustained Attention with Sustained Attention after training revealed significant improvement (x^2=-2.051, df1, $p<0.04$). Comparison of the baseline and after training data of Impulse Control, represented also significant improvement in inhibition (x^2=-2.203, df1, $p<0.028$).

Conclusions:ADHD is associated with impaired cortical network activity. The findings of this study suggest that proper regulation of cortical connectivity, based on individualized symptom tracking, is a promising approach for reducing symptoms of attention deficit and hyperactivity, by significant improvement of Sustained Attention and Impulse Control.

Correlation of neurocognitive symptoms and Vitamin B12 serum level in COVID-19 Patients

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Introduction: Post-COVID neurological symptoms may have the potential to predict longer term neurodegenerative diseases. Challenges of timely diagnosis and early treatment in the era of evidence based and personalized medicine is quite important. Cost–effective analysis shows benefits of timely diagnosis-reduced institutionalization costs, prolonged survival and delayed institutionalization.
At the beginning of the COVID-19 pandemic, olfactory and gustatory changes were commonly related with vitamin B12 deficiency. From early 2022, post-COVID neurologic symptoms significantly worsened patients' quality of life. Our research aimed to evaluate the correlation between vitamin B12 deficiency and post-COVID neurological symptoms.

Methods: We enrolled patients with laboratory-confirmed COVID-19 for our study, all of whom reported symptoms such as memory problems, impaired concentration, mood changes, tingling sensations, and/or muscle weakness. Standard enzyme-linked immunosorbent assay (ELISA) methods were used to measure serum vitamin B12 levels, along with CBC and TSH.

Results: We enrolled 312 patients. 288 (85%) of them showed low levels of vitamin B12 (below 200 pg/ml). A daily dose of oral vitamin B12 therapy for two months was prescribed. Those with severe deficiencies received injectable forms for the first ten days before switching to tablets. Post-treatment, all patients reported significant symptom reduction or complete improvement. After two months of treatment, the two groups were assessed for serum vitamin B12 levels. In Group 1 (oral dosage), 208 (85%) participant showed significant improvements in B12 levels, reaching around 300 pg/ml, and most neurological symptoms disappeared, with memory problems as the main remaining issue.
In Group 2 (combination therapy), 80 (90%) of participants achieved B12 levels near 400 pg/ml after the intramuscular and oral treatment. Despite this, most patients still had levels below the target of 450-500 pg/ml, though symptoms improved after just 14 days. We hypothesize that the overconsumption of vitamin B12 may be caused by COVID-19 (a result of physiological alterations caused by the illness, due to its interaction with one or more viral proteins).

Conclusions: We demonstrated an association between treatment with vitamin B12 and a reduction in neurological symptoms in patients with post-COVID symptoms. By understanding the impact of vitamin B12 deficiency on post-COVID neurological symptoms may inform a comprehensive approach to addressing both the immediate effects of COVID-19 and the ongoing challenges of neurodegenerative diseases.

Effect of Anesthetic Methods on Postoperative Cognitive Function in Patients Undergoing Nodular Goiter Surgery

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Introduction: The use of laryngeal mask (LM) in thyroid surgery allows anesthesiologists to avoid the use of myorelaxants against the background of inhalation anesthetics, benzodiazepines and narcotic analgesics used in general anesthesia. Postoperative cognitive dysfunction (POCD) is very common in patients undergoing surgery, with some data suggesting an incidence of more than 40%. To date, data are mixed as to whether anesthesia technique can affect patient outcome in terms of postoperative cognitive function (1). This study aimed to determine the degree of cognitive impairment in patients operated on for nodular goiter under general anesthesia with LM compared with general anesthesia with intubation.

Methods: The study was conducted on 60 patients who underwent thyroidectomy; in the main group, general anesthesia was performed using laryngeal mask airway (LMA), and in the control group, general anesthesia was performed using endotracheal intubation (ETI). To assess cognitive impairment, we used the Mini-Mental State Examination (MMSE) and the Stroop test administered before surgery and 7 days after surgery. During the same period, the frequency of delirium was assessed and functional status in terms of activities of daily living was recorded.

Results: Thirty patients received general anesthesia with LMA (main group) and 30 patients received ETI (control group). The results of neuropsychological testing showed that there were no significant differences between the groups on eight of ten neurocognitive tests at baseline and seven days after surgery. On day 7 postoperatively, a statistically significant decrease in the Instrumental Activities of Daily Living indicator was observed in the control group (24) 80% compared to the main group (26) 66%, ($p = 0.043$). A significant difference in the Stroop test was also observed in the control group (21 patients showed impairment) compared to the main group (two patients) at baseline ($p < 0.02$) and 7 days after surgery ($p < 0.03$). Postoperative delirium occurred in four patients (13.3%) in the study group and in six patients (20%) in the control group.

Conclusions: In patients with nodular goiter undergoing thyroidectomy, general anesthesia with the use of LM in the immediate postoperative period decreased the risk of cognitive decline compared to intubation anesthesia, although the groups differed at baseline.

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Self-reported post-Covid cognitive dysfunction in the general population of Georgia.

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Introduction: The coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11, 2020. To date, approximately 775 million cases of COVID-19 have been reported worldwide. The disease has long-term effects, collectively termed “Long COVID” or “Post-COVID” condition.

Post-COVID condition can affect multiple organ systems, with symptoms lasting weeks to even years after infection. Neurological symptoms are among the most common manifestations of Post-COVID, including headache, dizziness, myalgia, fatigue, and, more specifically, anosmia/phantosmia and ageusia/dysgeusia. Cognitive impairments, such as difficulty thinking or concentrating (“brain fog”) and minor memory disturbances, have also been frequently reported.

Data on the neuropsychiatric manifestations of Post-COVID among the Georgian population are limited. This study aimed to evaluate self-reported cognitive dysfunction in patients who have otherwise recovered from COVID-19.

Methods: A cross-sectional study was conducted in May 2024 using a self-report online questionnaire to assess the duration, severity, and quality of general and neurological COVID-19 symptoms across different age and gender groups. The study also evaluated self-reported cognitive function and psychiatric manifestations before and after a COVID-19 diagnosis. The manifestations were evaluated subjectively, with the questions focusing on comparing individually assessed cognitive function after the infection to its state before the diagnosis. This approach was necessary because data on cognitive assessments in the general population prior to COVID-19 were not available in Georgia.The Modified Fatigue Assessment Scale was used for cognitive self-evaluation. Descriptive and analytic statistical methods were employed to analyze the data.

Results: A total of 105 participants with PCR-confirmed COVID-19 completed the survey. Most participants (51%) reported their most recent COVID-19 infection occurred in 2022, and the most common number of infections per individual was one (50%).

During the acute infection phase, the most frequently reported symptoms were fatigue (79%), myalgia (72%), and headache (70%). In the Post-COVID period, 52% of participants continued to experience fatigue, and 46% reported developing memory problems.

Younger participants (aged 18–29) were more likely to report increased anxiety post-recovery (47.2%) compared to those aged 30–49 (23.3%) and >50 years (14.3%), with a statistically significant difference ($p<0.05$). Additionally, 41% of participants reported difficulty concentrating after recovery; however, differences based on age groups or the duration of COVID-19 symptoms were not statistically significant.

Conclusions: Neuropsychiatric manifestations play a significant role in patients with Post-COVID conditions. However, the long-term effects of the infection and the broader

psychological impact of the pandemic on the general population require further investigation in future studies.

GOMEZ-LOPEZ-HERNANDEZ SYNDROME: THE FIRST CASE STUDY OF PATIENT IN GEORGIA

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We present the first documented case of Gomez-Lopez-Hernandez Syndrome (GLHS) in Georgia, involving a 36-month-old Georgian male born to non-consanguineous parents. The patient was admitted to the clinic with a preliminary diagnosis of Autism Spectrum Disorder (ASD), confirmed through ADOS-2 (Autism Diagnostic Observation Schedule) and M-CHAT-R™ (Modified Checklist for Autism in Toddlers, Revised) assessments. Clinical observation revealed hallmark ASD symptoms, including lack of speech, disregard for social interaction, absence of eye contact, restlessness, aggression, and self-injurious behavior.

Concurrently, features characteristic of GLHS were identified, including bilateral parietal-temporal alopecia, brachyturricephaly (broad and tower-like cranial shape), low-set posteriorly retracted ears, right-eye strabismus, hypotonia (Beighton scale score: 6), and ataxia (difficulty in balance maintenance). Family history revealed no similar cases among close relatives.

MRI findings corroborated the GLHS diagnosis by demonstrating rhombencephalosynapsis (fusion of the cerebellar hemispheres with agenesis of the cerebellar vermis), mild dilation of the lateral ventricles, and an arch-like deformation of the corpus callosum. However, clinical evaluation did not identify trigeminal anesthesia, recurrent painless eye infections, corneal opacities, or ulcerated wounds on facial skin or buccal mucosa.

Based on current scientific literature, the presence of brachyturricephaly alongside rhombencephalosynapsis and bilateral parietal-temporal alopecia supports a diagnosis of GLHS. To our knowledge, this case represents a rare combination of GLHS and ASD, emphasizing the importance of recognizing overlapping syndromic features.

COGNITIVE DISFUNCTION IN PARANOID SCHIZOPHRENIA

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Aims: The study aimed to evaluate cognitive impairment associated with changes in cognitive functions caused by the schizophrenic process, focusing on patients with paranoid schizophrenia.

Methods:
Patients with paranoid schizophrenia were categorized into two groups based on the duration of their illness:

- **Group 1:** patients with paranoid schizophrenia of up to 3 years' duration.
- **Group 2:** patients with paranoid schizophrenia of up to 15 years' duration, where deficit syndromes such as apathy and abulia were prominently expressed in the clinical picture.

Cognitive impairments were classified into three main clinical categories:

1. Attention problems.
2. Memory pathology.
3. Impairments in executive functions.

Since there is no single standardized tool for diagnosing cognitive impairment, the following methods were used: memorizing 10 words, Kraepelin's tables, Bourdon's correction test, the Mini Mental State Examination (MMSE), the Global Deterioration Rating Scale, and the Wisconsin Card Sorting Test.

Results:
Forty-six patients were enrolled, 17 in Group 1 and 39 in Group 2. The research revealed that IQ was related to the duration of the disease, the length of schizophrenia episodes, and the number of episodes experienced during the illness and treatment.

The most common cognitive impairments included issues with concentration and the distribution of attention. High distractibility was observed, affecting both auditory and visual processing. The clinical picture of cognitive impairment was highly polymorphic and often involved a combination of deficits in thinking, memory, attention, and executive functions.

Cognitive impairments had a more profound impact on reducing patients' social adaptation levels compared to positive symptoms. These impairments were identified as key clinical predictors of disability.

Conclusions: Short illness duration (≤3 years): Cognitive impairments were mild and did not significantly affect daily functioning. Common symptoms included preserved awareness of intellectual and memory issues, increased fatigue, attention dispersion, and difficulties in assimilating new information. **Long illness duration (up to 15 years):** Cognitive impairments were severe, leading to significant social disintegration and maladjustment. Symptoms included difficulty recognizing the social context, an inability to retain short-term information, and challenges in selecting relevant information, often accompanied by an inability to differentiate between useful and irrelevant data.

Adeno-Associated Virus directed, Clustered Regularly Interspaced Short Palindromic Repeats-Associated Protein 9 guided, O6-methylguanine–DNA methyltransferase gene knockout and its effects on glioblastoma prognosis.

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Glioblastoma is the most malignant central nervous system tumor, accounting for 50% of all glial neoplasms. Despite advances in treatment, it remains largely incurable(1). Patients commonly experience seizures, memory loss, intense migraines, and significant personality changes.

Current standard treatments, including surgical resection followed by radiation therapy and chemotherapy, provide an average survival of only 15.3 months(2). We hypothesis a novel treatment approach that we believe will extend glioblastoma patients' survival to an average of 21.7 months (95% confidence interval, 17.4–30.4 months)(2).

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a system derived from a natural defense mechanism of bacteria and archaea, where it protects against invading viruses when combined with a series of CRISPR-associated (Cas) proteins by cutting their DNA. Our methodology employs the intravenous delivery of CRISPR-Cas9 DNA derived from *S. pyogenes*, encapsulated within Adeno-Associated Virus (AAV) vectors flanked by Inverted Terminal Repeat sequences(3)(4). By modifying the AAV capsid, we achieve specific targeting of astrocytes, the cells predominantly involved in glioblastoma(5)(6). The inability of AAV to replicate without a helper virus minimizes systemic adverse effects.

The 4.7 kb limit of the Adeno-Associated Virus vector genome enables the inclusion of multiple copies of specific double stranded DNA (dsDNA) required for Homology-Directed Repair and single-guide RNA (sgRNA)(7). Within the astrocytes, CRISPR-Cas9, guided by our selected sgRNA (sequence: 5'-CATCATAGGTCATCATGCTTAT-3'(8)(9) induces double-stranded breaks in the host DNA only if the R132H mutation of the *Isocitrate Dehydrogenase 1 (IDH1)* gene (CGT→CAT) is present 10–12 bases upstream of the Protospacer Adjacent Motif (PAM) sequence, that acts as a recognition signal for the CRISPR Associated Protein 9 (Cas9).(10)(11)

Homology-Directed Repair inserts our dsDNA sequence between Chi sequences in the host genome. Subsequent activation of the *IDH1* gene promoter leads to the production of incomplete IDH1 enzyme and a new sgRNA (sequence: GTGAAATGAAACGCACCACAC). The newly synthesized sgRNA directs CRISPR-Cas9 to target the *O6-Methylguanine-DNA Methyltransferase (MGMT)* gene, inducing continuous double-stranded breaks via Non-Homologous End Joining (NHEJ) until either a frameshift or nonsense mutation occurs, resulting in functional knockout of the MGMT enzyme.

This knockout renders tumor cells incapable of repairing alkyl group-induced DNA damage. When combined with Temozolomide and radiotherapy, this strategy induces apoptosis in neoplastic cells, increasing survival by approximately six months(12).

In summary, we propose a simple intravenous injection of modified AAV to disrupt MGMT function, enhancing the efficacy of chemoradiotherapy in glioblastoma patients.

Keywords: *MGMT, Glioblastoma, Adeno-Associated Virus, CRISPR-Cas9, Chemoradiotherapy.*

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Morphological Phenomenon of "Chemotherapy"- Induced Cognitive Impairment of Rats' Central Nervous System

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Introduction: Chemotherapy is an effective conventional treatment for cancer patients, but it is associated with serious short- and long-term neurological side effects. Neurotoxicity manifests with a wide range of symptoms including fatigue, emotional instability, anxiety, concentration difficulty, and issues with learning, reasoning, attention, and memory. Chemotherapy-induced cognitive impairment (CRCI), also known as "chemo-brain," occurs frequently during or after treatment.

Doxorubicin (DOX) is commonly used in adjuvant chemotherapy for various tumors, but its efficacy against brain tumors is limited due to its poor penetration of the blood-brain barrier (BBB). Despite this barrier, DOX has been detected in the brain following peripheral administration and can cause severe neurotoxicity. The exact morphological mechanisms underlying chemo-brain, however, remain unclear.

Methods: Our study investigates the effects of doxorubicin (DOX) in an acute experiment on the cerebral cortex and cerebellum, aiming to contribute to the understanding of the functional and morphological basis of DOX-induced neurotoxicity.

The experiment involved adult male Wistar rats (m=170-200 g). A control group of intact animals followed standard vivarium protocols (GALS regulation 2023), and four experimental groups received different doses of DOX (5-15 mg/kg) with varying numbers of injections. Histological and immunohistochemical studies were conducted.

Results: We focused on structural changes in the cortex and cerebellum, observing a significantly reduced number of intact neurons, along with phenomena such as swelling, shrinkage, eosinophilia, and "red neurons." Other findings included chromatolysis, neuronophagia, "crystal-like" cells, massive coagulative necrosis, and expanded Virchow-Robin spaces. Marked reactive gliosis, formation of neuritic plaques (β-amyloid protein), and "neurofibrillary tangles" (microtubule-associated tau-protein) showed progressive tendencies over a 15-day period. Additionally, we noted degeneration of astrocytic glial cytoskeletal elements, hypertrophy-hyperplasia of astrocytes with high expression of anti-GFAP, and in the cerebellum, swelling and disorganization of the Purkinje cell layer with strong positive anti-GFAP reactions. In the choroid plexus, findings included hyperemia, hemolysis, hemo- and plasmorrhagia, and marked swelling of the ependyma with a high positive anti-GFAP reaction.

Conclusions: Thus, a study of doxorubicin (DOX) effect showed significant changes in all neural elements of cytoarchitecture causing reactive astrogliosis and the formation of glial scars in the area of inflammation. These changes may be considered as an essential basis for chemo-brain and its associated cognitive impairment.

Medication safety in older patients with Cognitive Disorders: Best Practices and Innovations.

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Pharmacovigilance is defined by the World Health Organization as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem”. This activity is especially important in older people who are often excluded from clinical trials as they have multiple chronic conditions and use multiple medicines for longer durations than the clinical trials. The rising prevalence of cognitive disorders such as Alzheimer's disease and other forms of dementia poses significant challenges for pharmacovigilance. Effective drug safety monitoring is crucial in this vulnerable patient population due to their complex pharmacotherapy regimens and increased susceptibility to adverse drug reactions (ADRs). The challenges are unique in pharmacovigilance for cognitive disorder patients, including polypharmacy, communication barriers, and the underreporting of ADRs. The best practices in pharmacovigilance from European Medicines Agency (EMA/340669/2024) emphasized the role of comprehensive medication reviews, interdisciplinary care teams, and targeted education for healthcare providers, patients, and caregivers. These practices are essential for identifying and managing ADRs effectively. Innovative approaches are transforming pharmacovigilance, Artificial intelligence and machine learning are being leveraged to enhance ADR detection and analysis, while real-world data and big data analytics offer new insights into drug safety. Additionally, mobile health (mHealth) technologies and wearable devices are emerging as powerful tools for real-time monitoring and reporting ADRs. A key focus of reporting ADRs will be on pharmacology classes of drugs known to induce cognitive impairment. These include: Benzodiazepines and other Sedatives, Opioids, Antipsychotics, Antihistamines, and Antidepressants. Case studies of successful pharmacovigilance programs will be presented to illustrate the practical application of these innovations and best practices. These examples will underscore the potential for improved patient outcomes through proactive and informed pharmacovigilance efforts. Finally, we will look ahead to future directions in pharmacovigilance for cognitive disorders, considering emerging technologies, global collaboration, and the need for supportive policies and regulations. Healthcare professionals must contribute to safer, more effective medication use in cognitive disorder treatment. By integrating best practices with innovative approaches, we can enhance drug safety and improve the quality of life for patients with cognitive disorders.

Kay words: Pharmacovigilance, cognitive disorders, AI, ADRs, elderly

THE EFFECT OF INTRAVENOUS AMANTADINE SULFATE ON EARLY POSTOPERATIVE COGNITIVE FUNCTION IN LAPAROSCOPIC RADICAL PROSTATECTOMIES: A RANDOMİZED, DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL

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Introduction: Postoperative cognitive dysfunction (POCD), one of the most common complications in the geriatric patient group, leads to a prolonged hospital stay, functional insufficiency, and increased mortality and morbidity. Research on the prevention and treatment of POCD are ongoing. We investigated the effect of amantadine sulfate, which has a neuroprotective effect, on POCD in patients who underwent laparoscopic radical prostatectomy (LRP).

Methods: Patients undergoing laparoscopic radical prostatectomy were recruited to this double-blind trial and randomly assigned into 2 study groups, amantadine versus control. Before the operation, a standardized mini-mental state examination (SMMSE) was applied to all patients as per their educational status. Amantadine sulfate (200-mg intravenous (iv)) was administered to the amantadine group; the first dose was administered 12 h before the operation, the second dose 3 h before the operation; the control group received a saline infusion during the same period. SMMSE was repeated in both the groups at 24 and 48 hours postoperatively. Visual analog scale (VAS) values of the patients, analgesic consumption, and time-to-discharge were recorded. Changes in the preoperative and postoperative SMMSE scores were then compared between the groups.

Results: Forty-three patients were enrolled in this study, n = 19 in the amantadine group and n = 24 in the control group. No significant difference was noted between the groups in terms of patient characteristics, operative time, perioperative complications, postoperative pain, and analgesic consumption. SMMSE score decreased at least 1 point from baseline to 24 and 48h in 13 (54,2%) and 12 (50%) control patients and 4 (21,1%) and 3 (15,8%) amantadine group patients, respectively. The difference between the groups was statistically significant at $p< 0.05$.

Conclusions: In cases of preoperative amantadine sulfate administration, the incidence of POCD after laparoscopic radical prostatectomy was significantly lower. We thus believe that amantadine sulfate administration may be beneficial as a prophylactic in the patient group with a high risk of POCD, warranting further studies to determine the optimal dose.

Keywords: amantadine sulfate, postoperative cognitive dysfunction, laparoscopic surgery

Abstract was accepted but not presented at the meeting.

Awareness Under Anesthesia: Evidence from Clinical Trials

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An understanding of the clinical problem of "awareness under anesthesia" must begin with recognition that the powerful amnestic properties of anesthetics can readily create the illusion of a void of consciousness — but only because experience is forgotten. Thus posed is a difficult clinical and ethical question of whether we are concerned that patients have any form of conscious substrate while under anesthesia, or if our concern is reserved only for those circumstances in which an enduring memory is formed. Rigorous studies using the isolated forearm test found that 4.6% of all adults and 11% of those aged 18-40 have some form of connected consciousness during general anesthesia in a clinical setting, while highly controlled laboratory studies of propofol and dexmedetomidine infusions at doses leading to unresponsiveness found that 89.8% of subjects receiving dexmedetomidine and 73.5% of those receiving propofol reported some form of conscious experience during unresponsiveness. The current state of the literature suggests that some form of conscious substrate can occur in a small but non-zero percentage of patients under general anesthesia, but this is mostly highly internalized and not connected to external events or stimuli. The reported incidence of awareness under anesthesia in clinical settings depends dramatically on how the information is sought. Studies actively questioning for awareness using the modified Brice interview consistently report an incidence of 0.1 - 0.2% (1:500 – 1:1,000 cases), while those relying of self-report are more than an order of magnitude less, at 0.005 – 0.007% (1:15,000 – 1:20,000 cases). This wide discrepancy could be the result of under-reporting via self-report and over-reporting via targeted questioning, but the extent of each contribution is presently unclear. Prominent anesthetic risk factors include the use of neuromuscular blockade, rapid sequence induction, and total intravenous anesthesia (TIVA), while surgical risk factors include obstetric and cardiothoracic procedures. Of particular concern is the ability for awareness under anesthesia to lead to psychological morbidity, including the development of post-traumatic stress disorder (PTSD). The presence of pain and paralysis during the awareness event are most strongly correlated to psychological distress, and psychological distress at the time of the awareness event is most predictive of long-term psychological harm. Reports from awareness trials have found that 43% of patients experiencing awareness will screen for PTSD symptoms postoperatively (compared to 16% of those without awareness), while 14.3% will meet full PTSD diagnostic criteria (cf. 7.6%). A series of large randomized controlled trials conducted through the 2000s and 2010s found that the use of processed electroencephalography (pEEG, usually the bispectral index, BIS) in the titration of anesthesia was not superior to following end-tidal concentrations of anesthetic gases in the case of general anesthesia using volatile gases. However, the use of pEEG is superior to routine care in the case of general anesthesia administered by TIVA. In cases of definite awareness, referral to psychological or psychiatric expertise is highly advised. Several significant questions in this clinical domain remain, including whether awareness without recall can cause psychological harm, and whether there is a genetic predisposition to awareness.

Study of the Effects of Dopamine and Melatonin on Cognitive Function and Sleep-Wake Cycles Due to Late-Night Phone Use

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Background: The widespread increase in smartphone usage, particularly among teenagers, has led to growing concerns about phone addiction and its implications for cognitive health. Dopamine, a neurotransmitter involved in memory, arousal, and emotional regulation, plays a critical role in addiction mechanisms. Conversely, melatonin, the hormone responsible for regulating sleep and maintaining circadian rhythms, is influenced by light exposure. The interaction between these two neurotransmitters is central to cognitive function and sleep quality.

Methods: This study explores the relationship between dopamine and melatonin and their combined impact on cognitive function and sleep cycles, particularly as disrupted by late-night screen use. We hypothesize that increased dopamine activity in the prefrontal cortex, triggered by late-night phone usage, interferes with melatonin's regulatory effects on sleep, resulting in cognitive impairments. Students from the University of Georgia were selected using the Social Networking Addiction Scale (SNAS) and the Pittsburgh Sleep Quality Index (PSQI). Electroencephalography (EEG) was used to monitor in the brain activity across different sleep stages Dopamine and melatonin levels will be measured through positron emission tomography (PET) scans and saliva assays, respectively. Statistical analyses were conducted using SPSS.

Results: Fifty students were enrolled, mean (SD) age was 21.0 (1.5) and there were 31/50 (62%) males. Questionnaire findings revealed that most participants engage in late-night social media use before bed. Poor sleep quality was prevalent, as indicated by an average PSQI score of 7.64. A positive correlation (r=0.45) between SNAS and PSQI scores suggests that higher social media addiction is significantly associated with poorer sleep quality (β=0.65; CI:0.42,0.88; p=0.002), potentially leading to cognitive impairments and reduced well-being. Based on the SNAS scale, 63.9% (32 participants) were classified as non-addicted, while 36.1% (18 participants) were classified as addicted to social networking sites. Increased beta activity during sleep indicated heightened brain arousal and fragmented sleep, correlating with difficulties in attention and memory retention. Reduced slow-wave (delta wave) activity was associated with impaired declarative memory and overall cognitive dysfunction.

Conclusions: This disruption in sleep architecture has been shown to correlate with cognitive impairments, including reduced attention span, memory deficits, and overall cognitive dysfunction The study provides preliminary data demonstrating the detrimental effects of late-night phone usage on cognitive health and sleep quality. Understanding this complex interplay is critical for developing interventions to mitigate the adverse effects of late-night electronic device use on cognitive health.

Self-awareness discrepancies among MCI patients in Georgia

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Introduction: Dementia, as one of the leading challenges of the modern healthcare system, is associated with the decline in different areas of cognitive function and the inability to carry out complex, as well as basic daily activities. Patients with Mild Cognitive Impairment (MCI) as the ultimate precondition of dementia tend to show no decline in complex daily activities based on DSM V. However, there are several questioning the self-awareness of MCI patients.

Methods: This research is a part of a 7-year longitudinal community-based study conducted to identify the cognitive changes over time among a population of Georgian individuals aged 40 years or older. During a second phase of the study participants were randomly chosen for follow-up. To assess participants' cognitive abilities, Montreal Cognitive Assessment (MoCA) test was used. The Instrumental Activities of Daily Living was assessed by patients themselves and by their caregivers in parallel to observe any discrepancies.

Results: We enrolled 103 participants, of whom 52 had dementia and 51 had MCI. There were 62 (60.2 %) males. ANOVA was used to determine a statistically significant difference between the aMCI, naMCI, and dementia groups reported by the patients themselves and their caregivers/family members.

Performing t-test, showed that caregivers/family members reported significantly more decline in everyday functioning, compared to the self-report among dementia group (mean=4.6, t=-10.21 $p< 0.0001$), among the aMCI group (mean= 1.5, t=-5.23, $p<0.002$) and among the naMCI group (mean= 0.4, t=-6.57, $p<0.001$).

Discussion: Based on DSM V criteria, patients with MCI tend to show no decline in complex daily activities; however, the result of the present study stated that the patients with MCI also show some degree of decreased self-awareness while comparing the results of their self-reports and the results of their caregiver/family members.

This difference was statistically significant, indicating the MCI patients, and especially the aMCI subgroup, had some level of decreased self-awareness regarding their everyday functioning.

These results may be explained by the fact that patients with any kind of cognitive decline have a tendency to underestimate their functional losses compared to the responses of their caregivers/family members.

Conclusions: MCI patients, and especially the aMCI subgroup, had some level of decreased self-awareness regarding their everyday functioning compared with caregivers/family members responses. This demonstrates the need to collect data regarding patients' daily activities from an informant when considering care pathways.

Perioperative Neurocognitive Disorders: Clinical Impact and Biomarker Insights

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Perioperative Neurocognitive disorders (PND) include delirium and disorders of memory and thinking of varying degrees of severity and duration (Neurocognitive Disorders (NCD)). Importantly these predominantly affect the older patient (65 years or over) and are the most frequent postoperative complication in this age-group. Delirium occurs in 10 to over 50% of elderly patients in their first week after surgery, and postoperative NCD is found in similar numbers but persisting in approximately 10 – 15% of patients for at least 12 months. The acute impacts can be personally distressing and frustrating, but they also are associated with increased complications, length of hospital stay, need for higher degrees of supportive care and so impact successful surgical recovery.(1) Of significant concern is the association of delirium and postoperative NCD with increased mortality and the progression of longer-term cognitive decline, including dementia.(2) This has huge impacts on the person, their family and carers, and healthcare resources. It should always be kept in mind, however, that cognitive outcomes are usually excellent for most patients, especially those with high function and no or minimal pre-existing cognitive impairment.

Currently, our understanding of the underlying mechanisms of delirium and NCD is still fragmentary. Most strategies for care involve detection of risk, implementation of multi-component protective strategies, avoidance of precipitating factors, and early and active support and rehabilitation. Such programs have been shown to reduce delirium, falls and length of stay in 40% of at-risk patients.(3)

Research into objective indictors of delirium and postoperative NCD is aimed at identifying risk and providing early diagnosis and is also importantly helping to establish an understanding of their pathology. Neural imaging (such as fMRI and PET scanning) is very informative but not accessible routinely. Likewise, EEG monitoring is only usually available in certain research settings, except for the opportunities provided during anaesthesia care (processed EEG (pEEG)). Whilst pEEG is readily available, it provides, to date, only limited information and still uncertain associations with delirium and NCD following anesthesia.

A currently favored hypothesis is that a vulnerable brain is susceptible to systemic inflammation which drives neuroinflammation and neuronal functional and physical injury.(4) These changes may induce short term vulnerability to disturbances in cortical connectivity, attentiveness and short-term memory. This can lead to acute disturbances such as delirium and delayed neurocognitive recovery (dNCR), and possibly an acceleration of a decline trajectory affecting long-term cognition. Plasma and CSF biomarkers of interest include those associated with systemic inflammation (eg Interleukin-6, TNF-alpha and CRP), neuroinflammation (glial fibrillary acid protein (GFAP), s-100-beta), neuronal injury (eg Neurofilament light (NfL)), and Alzheimer's disease (amyloid beta 42 and 40, total tau, phospho-tau (p-tau) 181 and p-tau 217). Connecting the dots is complex, but current data suggests that pre-existing biomarkers of Alzheimer's disease, neuronal injury and/or inflammation carry increased risk of delirium and possibly postoperative NCD.(5) Post-operatively, forms of PND are associated in some studies with higher levels of IL-6, CRP and subsequently NfL.(6,7) This is providing some support for the 'neuroinflammatory' hypothesis.

In future, the aim will be to specifically target and prevent neuronal stress and injury. This may be achieved by including 'neuro-protective' measures during anesthesia and acute hospital care. There will likely not be a single 'magic-bullet' but rather a range of strategies and interventions we can use to make the perioperative journey cognitively safer.

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