When and why do psychosis patients discontinue antipsychotics? A data-driven approach using artificial intelligence [Abstract]

F. Coutts, S. Mena, Alkomiet Hasan, I. Winter-van Rossum, W. W. Fleischhacker, R. Kahn, M. Davidson, I. Sommer, N. Sirbu, G. Jacobs, L. Bryant, L. Moles, N. Koutsouleris, P. A. Lalousis

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CHALLENGES IN SCREENING AND DIAGNOSING PREMENSTRUAL DYSPHORIC DISORDER: FINDINGS FROM A DUAL-APPROACH STUDY IN HUNGARY

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Introduction: Premenstrual dysphoric disorder (PMDD) is an underdiagnosed mood disorder linked to the premenstrual phase [1,2]. Current diagnostic guidelines recommend prospective daily symptom ratings over at least two menstrual cycles, which places a considerable burden on both patients and healthcare providers. Screening questionnaires may offer a partial solution by identifying individuals with probable PMDD [3]. This study aimed to evaluate and compare the applicability of a prospective daily symptom rating scale and a retrospective screening questionnaire to improve the recognition of PMDD in clinical practice [4,5].
Methods: The study was performed at three timepoints: first, retrospective data collected from 230 healthy women; second, prospective data from 28 women in their premenstrual phase; third, data from the same women in their follicular phase. At the first timepoint probable PMDD was assessed using the retrospective DSM-5 Based Screening Tool [5], while anxio-depressive symptoms and well-being were evaluated using the Beck Depression Inventory, the state subscale of the State-Trait Anxiety Inventory, and the WHO Well-Being Scale. In the prospective assessments, the Daily Record of Severity of Problems questionnaire (DRSP) [4] and the above-mentioned psychometric questionnaires were completed.
Results: In the first phase, the sample was divided into women who screened positive (PMDD group, n=144) and negative (nonPMDD group, n=56) for PMDD determined by the DSM-5-Based Screening Tool. The PMDD group reported significantly more severe anxio-depressive symptoms (U=2578,5;z=-7,408;p<0,001; t(228)=-4,973,p<0,001) and lower well-being (U=4773,z=-2,926,p=0,003) compared to the non-PMDD group. These symptoms were more pronounced in the PMDD group during the premenstrual phase, particularly regarding state anxiety (F(1,131)=4,152,p=0,044).
In the second and third assessments, the sample was categorized into women with a probable diagnosis of PMDD (PMDD group, n=9), and those without PMDD (nonPMDD group, n=19) based on the DRSP. Retrospective screening identified 17 individuals, whose probable PMDD diagnosis was confirmed by the DRSP. Regarding inconsistent classifications (n=11), the majority (n=10) screened positive for PMDD retrospectively, but did not meet the diagnostic criteria according to the DRSP. This discrepancy likely contributed to the lack of a statistically significant association between classifications based on the Screening Tool and the DRSP (p=0.061).
Across the entire sample, anxiety symptoms were more severe during the premenstrual phase (F(1)=10,09,p=0,004). Women with PMDD reported significantly more severe anxio-depressive symptoms (F(1)=9,82,p=0,004; F(1)=13,92,p=0,001). In this group, both anxio-depressive symptoms and reduced well-being were significantly more pronounced in the premenstrual phase (F(1)=16,93,p<0,001; F(1)=6,19,p=0,02; F(1)=5,73,p=0,024).
Conclusions: PMDD was associated with more severe anxio-depressive symptoms and reduced well-being both retrospectively and prospectively. Despite retrospective screening being more practical for routine clinical use, it tended to overestimate premenstrual symptoms. Moreover, fewer than 10% of participants from the retrospective phase continued into the prospective phase, reflecting the lower feasibility of prospective assessment. These findings highlight the challenges of accurately diagnosing PMDD using both retrospective and prospective methods and underscore the need for more efficient approaches in clinical practice.
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Conflict of interest
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WHEN AND WHY DO PSYCHOSIS PATIENTS DISCONTINUE ANTIPSYCHOTICS? A DATA-DRIVEN APPROACH USING ARTIFICIAL INTELLIGENCE

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Antipsychotic medication is the primary treatment for psychotic disorders, yet nearly half of individuals experiencing a first episode of psychosis discontinue treatment within one year against clinical guidance [1]. Discontinuation may result from poor insight, substance use, negative attitudes toward medication, side effects, cognitive difficulties, or the belief that treatment is no longer needed [2, 3]. Understanding which patients are most at risk of stopping medication, and why, is essential for informing clinical decisions and developing targeted interventions. However, most clinical trials rely on "all-cause discontinuation" (ACD) as a primary endpoint, which aggregates diverse reasons for stopping treatment or leaving the trial and lacks explanatory power. To address this gap, we applied an artificial intelligence (AI)-based clustering approach to identify subgroups of patients with shared characteristics in terms of symptom severity, side effect burden, and medication attitudes at the point of discontinuation. We then trained predictive models using baseline clinical and sociodemographic data to explore whether these subgroups could be identified earlier in care.
Data were drawn from 280 individuals with schizophrenia enrolled in the European Long-Acting Antipsychotics in Schizophrenia Trial (EULAST; NCT02146547) trial [4]. For patients labelled as discontinuing their medication or the trial (ACD), data from the nearest visit within two months of discontinuation were used. Measures included the Clinical Global Impressions (CGI) scale, Positive and Negative Syndrome Scale (PANSS), Medication Adherence Report Scale (MARS), Systematic Monitoring of Adverse events Related to Treatment System (SMARTS), Subjective Wellbeing under Neuroleptic Treatment Scale (SWN), and the digit symbol task from the Wechsler Adult Intelligence Scale (WAIS). We used orthogonal non-negative matrix factorization to identify patient clusters and applied multiclass Support Vector Machine models to predict cluster membership compared to no discontinuation based on baseline clinical and sociodemographic data. We also modelled two standard trial outcomes, ACD and symptomatic remission criteria [5], for comparison.
Of the total sample, 44.2% (n=124) discontinued their medication. Clustering revealed two distinct groups: a "Less Impaired" cluster (n=86), defined by more positive views of medication and better functioning, and a "More Impaired" cluster (n=38), characterized by greater illness severity, more side effects, and more negative attitudes toward medication ($p < 0.0001$). Baseline predictive models distinguished the More Impaired cluster from the Less Impaired (AUC =

0.64) and from the Non-Discontinuation group (AUC = 0.65). The Less Impaired cluster versus Non-Discontinuation comparison was less accurate (AUC = 0.60). All cluster-based predictions outperformed the ACD prediction (AUC = 0.59), but none exceeded the performance of remission prediction (AUC = 0.73).
This study identified two clinically meaningful subgroups of patients who discontinued treatment, with the More Impaired cluster showing worse symptoms and side effects and being more reliably predicted from baseline characteristics. These findings highlight the potential of AI-driven approaches to move beyond traditional trial endpoints and identify individuals at risk for discontinuation, opening the door to proactive, targeted interventions in early psychosis care.

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AI-BASED NEUROANATOMICAL PREDICTION OF INDIVIDUAL CYTOKINE PROFILES IN SCHIZOPHRENIA

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Background: Schizophrenia is a heterogeneous disorder characterized by significant variability in symptomatology, disease progression, and treatment response. Emerging evidence implicates immune dysregulation, particularly elevated pro-inflammatory cytokines, in its pathophysiology. Understanding the relationship between specific cytokines and brain structural alterations may offer insights into personalized treatment strategies.
Objectives: This study aimed to investigate whether structural neuroimaging data could predict individual cytokines in patients with schizophrenia using machine learning techniques, thereby elucidating the neuroimmune interactions underlying the disorder.
Methods: We analyzed data from 185 individuals diagnosed with schizophrenia from the Australian Schizophrenia Research Bank. Structural MRI scans were processed using the CAT12 toolbox in SPM, extracting grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) volumes across 136 neuroanatomical regions defined by the Neuromorphometrics atlas. Peripheral blood samples were assayed for nine cytokines: CRP, IFN-γ, IL-1β, IL-2, IL-6, IL-8, IL-10, IL-12p70, and TNF-α. Cytokine levels were log-transformed and dichotomized into high and low groups based on median splits. Support Vector Machine classifiers were trained using NeuroMiner (MATLAB) within a pooled 5-fold cross-validation framework with 10 permutations. Models were adjusted for age, sex, site, and total intracranial volume. Feature selection involved principal component analysis to reduce dimensionality, and model performance was assessed using balanced accuracy, area under the receiver operating characteristic curve, sensitivity, specificity, and permutation-derived p-values.
Results: Five cytokine models demonstrated statistically significant classification performance. The IL-1β model achieved a balanced accuracy (BAC) of 61.1% and an AUC of 0.60 ($p = 0.001$), with predictive features predominantly located in cerebrospinal fluid (CSF) and grey matter volumes (GMV) of posterior and cerebellar regions. The IFN-γ model yielded a BAC of 58.4% and an AUC of 0.60 ($p = 0.009$), with key predictors found in GMV of frontal, temporal, and subcortical areas. The CRP model reached a BAC of 56.7% and an AUC of 0.55 ($p = 0.003$), drawing on widespread GMV alterations across frontal, temporal, parietal, and subcortical regions. The IL-6 model produced a BAC of 58.9% and an AUC of 0.62 ($p = 0.010$), with relevant features located in both GMV and white matter volumes (WMV) of the frontal, temporal, and parietal lobes, as well as subcortical structures. Finally, the IL-12p70 model achieved a BAC of 60.0% and an AUC of 0.61 ($p = 0.005$), with predictive features spanning GMV, WMV, and CSF compartments across frontal, parietal, occipital, temporal, and subcortical brain regions.
Voxel-based morphometry analyses of misclassified individuals revealed distinct grey matter volume patterns, with frontal and temporal lobes consistently involved across cytokines. Subcortical structures and ventricular enlargement were notably associated with IFN-γ, IL-6, and IL-12p70, while cerebellar and cingulate regions were frequently implicated, underscoring their roles in cognition, emotion, and immune regulation.
Conclusions: This study advances our understanding of immune-brain interactions in schizophrenia by showing that individual cytokines, including less-studied markers like IL-12p70, are associated with distinct neuroanatomical patterns. Our findings highlight the mechanistic heterogeneity of immune involvement in schizophrenia and suggest that peripheral inflammation maps onto specific structural brain alterations.

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IMPROVING THE INTERPRETABILITY OF NEUROIMAGING BASED CLASSIFIERS FOR DEMENTIA(S) WITH DIFFUSION-BASED COUNTERFACTUALS

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Machine learning techniques, particularly deep neural networks, offer substantial promise for neuroimaging applications but remain hindered by opaque decision processes that impede clinical adoption. Brain diseases such as dementia present heterogeneous symptoms, comorbidities and subtle structural changes that challenge black-box classifiers. Explainable artificial intelligence (XAI) methods aim to enhance transparency and foster clinician trust; however, validating XAI method for neuroimaging tasks such as saliency-based ones is difficult in the absence of anatomical ground truth.
This study aims to validate saliency-based XAI methods by developing a counterfactual framework based on denoising diffusion probabilistic models (DDPMs). We hypothesize that DDPM-based inpainting of salient regions yields more realistic healthy counterfactuals and consequently provides a more objective evaluation of explanation quality than classic occlusions techniques for conterfactuals creation.
For preliminary experiments, T1-weighted magnetic resonance imaging (MRI) scans were gathered from 2098 subjects (1097 dementia patients, including Alzheimer's disease, frontotemporal dementia, primary progressive aphasia and dementia with Lewy bodies; 1001 healthy controls) among different source. A three-dimensional convolutional neural network was pretrained to distinguish patients from controls [1]. Saliency maps were generated using layer-wise relevance propagation (LRP) and the most salient three-dimensional patches per scan were identified at relevance percentile thresholds from 0.9 to 0.5. A DDPM trained on 7803 healthy scans on the whole age range was used to inpaint these patches with reconstructed healthy tissue. Prediction probabilities for non-healthy scans were compared between DDPM inpainting and three different occlusion techniques - uniform random noise, mean brain and blank - at each threshold. Statistical comparisons were performed using paired t-tests and Wilcoxon signed-rank tests to assess confidence decrease behaviour and differences in mean probability changes across methods and thresholds (α=0.05).
The DDPM achieved an out-of-sample normalised mean squared error on inpainted voxels of $6.0 \times 10{-}2$ ($\pm$ $2.4 \times 10{-}2$), peak signal-to-noise ratio of 32.8 ($\pm$ 4.9) and structural similarity index loss measure of $2.5 \times 10{-}2$ ($\pm$ $1.8 \times 10{-}2$), indicating high reconstruction fidelity. On the external test cohort of 253 dementia patients, DDPM inpainting produced a monotic decreasing mean confidence from the initial mean prediction on demented patients, with the