CLINICAL TRIAL PROTOCOL

Title: Multimodal Biomarker Predictors of Relapse in Major Depressive Disorder: A Hybrid Retrospective–Prospective Cohort Study

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1. Brief Summary

At the first step of treatment for Major Depressive Disorder, second-generation antidepressants (selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors) and/or psychotherapies with evidence-based efficacy are recommended (American Psychological Association, 2019).
It is clear and well documented that antidepressants prevent relapse in depression; however, it should also be remembered that 20% of individuals who continue taking medication still relapse within the first year, and 40% of those who discontinue the medication relapse (Kato et al., 2021). Therefore, there is no clear consensus regarding the optimal duration of treatment, and it is often suggested that, if possible, treatment should be continued lifelong. Although the long-term use of antidepressants is associated with relatively low side-effect profiles, half of patients report these effects as bothersome (Cascade et al., 2009). In our meta-analysis, clinical and demographic variables such as age, sex, and treatment resistance were examined as potential predictors of relapse in depression, but no factor that reliably predicted relapse could be identified (Arıkan et al., 2023).

Considering that the therapeutic effect of antidepressants can also be observed through the normalization of physiological parameters disturbed by depression, it is assumed that predictors of relapse may not be clinical or demographic but rather **biological, electrophysiological, and genetic markers**.

Previous studies have reported that electrophysiological markers such as P300 amplitude and latency, REM sleep latency, or frontal alpha asymmetry differ between healthy individuals and patients with MDD (Arıkan et al., 2023b; Arıkan et al., 2024). Therefore, these markers are considered potential indicators that could be used to guide the discontinuation of antidepressant treatment in patients. In the genetic field, the majority of research consists of RNA and small RNA studies (Wang et al., 2022; Ding et al., 2023). However, to date there has been no study in which an untreated patient group was followed to show the acute and chronic effects of medication use, and thus no biomarker has been defined to determine when an antidepressant can safely be discontinued.

This hybrid clinical study aims to identify biological, electrophysiological, sleep-related, and genetic biomarkers that can predict relapse following antidepressant discontinuation in patients with Major Depressive Disorder (MDD). The project integrates (1) a retrospective cohort with known recurrence outcomes, (2) a prospective cohort followed from treatment initiation through remission and medication discontinuation, and (3) a healthy control group providing normative biomarker values.

We hypothesize that relapse risk is associated with failure of biological normalization, even when clinical remission is achieved.

2. Detailed Description of Study Design

2.1. Participants

The study is conducted as a single-center investigation at the Kemal Arıkan Psychiatry Clinic in Istanbul, Turkey. All participants will be recruited from patients who present to the clinic and receive a DSM-5 diagnosis of Major Depressive Disorder (MDD).

Study Type

Observational / Prospective & Retrospective Hybrid Cohort
(Non-interventional; naturalistic antidepressant treatment continuation according to guidelines.)

Study Groups

Group A – Retrospective Cohort (Known Recurrence Status)

- Patients previously diagnosed with MDD
- **Known**: Recurrent vs. Non-recurrent phenotype
- **Single timepoint data available (T0)**
- Biomarkers obtained: qEEG, P300, REM latency, MRI, Genotype, RNA/miRNA
- Purpose: Identify trait-level baseline differences between recurrent and non-recurrent groups.

Group B – Prospective Cohort (Unknown Recurrence Status)

Participants newly entering treatment and followed for ~18 months:

Measurement Timeline:

- **T0 – Baseline**: qEEG, P300, REM, full RNA, miRNA, methylation, length of DNA, Genotype, HDRS-17, HARS, MMSE, WHOQOL-BREF, DASS-21. For a subgroup MRI-DTI will be received.
- **Treatment**: Antidepressant per clinical guidelines
- **T1 (4–8 weeks)**: Early change: qEEG + P300, HDRS-17, DASS-21
- **T2 (≥6 months of remission)**: Before discontinuation → **Full biomarker battery**
- **T3 (6 months medication-free)**: Full biomarker battery; relapse vs. no relapse determined

Group C – Healthy Control Group

- Single-timepoint biomarker acquisition: qEEG, P300, REM, full RNA, miRNA, methylation, length of DNA. For a subgroup MRI-DTI will be received.
- Normative reference for defining “biological normalization”

3. Objectives

Primary Objective

To determine whether **post-treatment normalization** of neurophysiological (EEG/P300, REM sleep), genetic (genome, transcriptome, small RNA), and neuroimaging (MRI) biomarkers predicts **relapse** following antidepressant discontinuation.

Secondary Objectives

1. Compare baseline (trait) biomarkers between:
    - Recurrent MDD
    - One-episode/non-recurrent MDD
    - Healthy controls
2. Evaluate whether **early changes** (T0 → T1) in EEG/P300 predict long-term relapse.
3. Examine whether **persistent deviations** from healthy biomarker ranges at T2 are associated with recurrence at T3.
4. Build a **Clinical Decision Algorithm** for “When to Safely Stop Antidepressants” based on multimodal biomarker normalization.

4. Hypotheses

H1 (Trait Differences)

At baseline, patients with a recurrent course show:

- Abnormal qEEG patterns
- Prolonged P300 latency / reduced P300 amplitude
- Shortened REM latency
- MRI structural/functional deviations
- Distinct RNA/miRNA signatures
  Compared to non-recurrent patients and healthy controls.

H2 (State Normalization Differences)

Prospective patients who **do not relapse** will show:

- Biomarker normalization at T2 (prior to discontinuation) to levels **not different** from healthy controls.

Relapsing patients will show:

- Persistent abnormalities at T2 despite clinical remission.

H3 (Early Change Predicts Outcome)

T0 → T1 improvements in qEEG spectral power and P300 parameters predict remission stability at T3.

5. Outcome Measures

Primary Outcome

Relapse Status at 6-month drug-free follow-up (Yes/No), defined via structured clinical interview and HAM-D score higher than 7.

Primary Biomarker Predictors

- qEEG spectral power (delta, theta, alpha, beta, gamma)
- P300 latency/amplitude
- REM latency (Sleep Profiler)
- Whole-genome SNV/CNV structural markers
- Transcriptome & small RNA signatures
- Long-read structural variant resolution: large insertions, deletions, repeats, fusions)
- Allele-specific methylation patterns (5mC)

Secondary Outcomes

- Early treatment response (T0 → T1 EEG/P300 change)
- Clinical scales: HAM-D, HAM-A, CGI, BPRS, WHOQOL-BREF, PSS, DASS-21
- MRI volumes/connectivity

6. Eligibility Criteria

Inclusion

- DSM-5 Major Depressive Disorder diagnosis

- Age 18+
- No neurological or major psychiatric comorbidity except anxiety

Exclusion

- Hearing impairment (P300 auditory oddball paradigm)
- Diabetes mellitus (EEG artifact risk)
- Medications affecting REM sleep

7. Study Procedures

The primary measurements will include resting-state brain activity recorded with quantitative EEG, P300 amplitude obtained from event-related potentials using an auditory paradigm, REM sleep latency measured with a portable EEG device, and depression severity assessed with the Hamilton Depression Rating Scale.

Genetic measures will be obtained by analyzing total RNA (transcriptome) and small RNA (miRNA) from blood samples collected before medication use in healthy individuals and in patients with Major Depressive Disorder, and by determining changes in these RNAs after medication use. Following conventional discontinuation of the medication, the expression levels of these RNAs will be reassessed either at one year or at the time of relapse, whichever occurs first. In addition, genomic data obtained from patients will be used for secondary analyses of different genomic variations and the associated genes. The genomic data will be analyzed in terms of disease etiology and medication choice (pharmacogenetics).

7.1. Parameters

Resting-State Quantitative EEG

Quantitative EEG (qEEG) refers to the numerical analysis of EEG data. When EEG signals are subjected to spectral analysis, we speak of quantitative EEG. Spectral analysis transforms any time series into the frequency domain. After raw EEG data are subjected to spectral analysis, they must be compared with a control group or a normative database; this is termed normative EEG. In our study, qEEG data obtained from the healthy control group will constitute the normative database and will be used to compare the current state of patients with depression.

P300 Wave Amplitude

The P300 wave is an electrophysiological parameter that provides information about the status of an individual's cognitive functions. It is measured with EEG. The P300 wave reflects the brain's discrimination response when a person hears or sees an infrequent, unfamiliar stimulus. A prominent P300 wave (higher P300 amplitude) indicates that cognitive functions such as

attention and reasoning are in good condition. Our meta-analysis showed that P300 amplitude is lower in patients with depression than in healthy controls (Arıkan et al., 2024). Other studies have reported that this abnormality improves with treatment (Zhong et al., 2019).

REM Latency

REM (rapid eye movement) sleep is the stage in which we dream. It is measured with sleep EEG. Our systematic review and meta-analysis demonstrated that the time to enter REM sleep (REM latency) is shortened in patients with depression (Arıkan et al., 2023). Some studies have shown that REM latency normalizes in patients whose depression is treated (Pillai et al., 2011).

Genetic Parameters

Multiple factors contribute to the development of depression, one of which is gene–environment interaction. Life events and stress can increase the expression of certain genes while silencing others. MicroRNAs (miRNAs) play a key role in regulating gene expression. In the literature, analyses of blood samples have reported that several miRNAs are differentially expressed in individuals with depression compared with controls (Maffioletti et al., 2016). Certain microRNA polymorphisms have also been associated both with depression and with the P300 wave (Xu et al., 2010). Finally, studies in patients receiving antidepressants have reported that expression levels of miR-124 and miR-132, which were previously high, decrease with treatment, whereas the low expression of miR-16 increases (Ahmadimanesh et al., 2023).

Techniques to Be Used

1) Clinical Interview

Psychiatric assessment will be conducted in accordance with the *Structured Clinical Interview for DSM-5 Disorders* (SCID-5; First et al., 2016). Depression severity will be assessed before and after treatment using clinical scales that are routinely administered in the clinic. The scales to be used are described below.

2) Hamilton Depression Rating Scale (HAM-D)

The HAM-D was developed by Hamilton (1960) to assess depression severity. In a semi-structured interview, the clinician inquires about depressive symptoms experienced during the previous week. Among the different versions, the 17-item form will be used in the present study. Some items are scored from 0 to 4, some from 0 to 2, and some from 0 to 3. The maximum total score is 53; scores ≥29 indicate severe depression, 16–28 moderate, 8–15 mild, and 0–7 no depression (Williams, 1988). The Turkish adaptation and reliability–validity study were conducted by Akdemir et al. (1996), yielding an internal consistency coefficient of .75. A **≥50% reduction** in HAM-D score will be used as the criterion for treatment response (Cusin et al., 2010).

4) Hamilton Anxiety Rating Scale (HAM-A / HARS)

The Hamilton Anxiety Rating Scale was developed by Max Hamilton (1959) to assess anxiety severity. In a semi-structured interview, the clinician inquires about anxiety symptoms experienced in the previous 72 hours. The scale consists of 14 items, each scored from 0 to 4. The maximum total score is 56; scores ≥31 indicate severe anxiety, 25–30 moderate to severe, 18–24 mild to moderate, and ≤17 mild anxiety (Maier et al., 1988). The Turkish adaptation and reliability–validity study, with an internal consistency coefficient of .72, was performed by Yazıcı et al. (1998).

5) Brief Psychiatric Rating Scale (BPRS)

The BPRS is an 18-item scale developed to assess symptom severity in psychiatric disorders (Overall & Gorham, 1962). It is completed by a trained interviewer. It is used to evaluate the severity of psychiatric disorders and to monitor the course of illness. Each item is scored from 0 to 6 according to symptom severity. Total scores range from 0 to 108, with higher scores indicating more severe psychopathology. The Turkish adaptation was carried out by Soykan (1990).

6) Clinical Global Impression (CGI)

The Clinical Global Impression scale is a clinician-rated instrument used to evaluate illness severity, degree of improvement, and response to treatment. It was developed by Guy in 1976 (Guy, 1976). It was initially designed for psychiatric disorders but is now widely used in other medical fields. The CGI typically consists of three main components:

- **CGI-Severity (CGI-S):** Rates the current severity of the illness from 1 (normal, not at all ill) to 7 (among the most extremely ill patients).
- **CGI-Improvement (CGI-I):** Rates change over the course of treatment from 1 (very much improved) to 7 (very much worse).
- **CGI-Efficacy Index (CGI-E):** Evaluates the overall response to treatment relative to side effects, rated from 1 (very favorable) to 4 (poor).

7) World Health Organization Quality of Life – Short Form (WHOQOL-BREF)

The WHOQOL-BREF is a comprehensive scale developed by the World Health Organization to assess well-being and enable cross-cultural comparisons. Following pilot studies conducted at 15 centers worldwide, the 100-item WHOQOL-100 and the 26-item WHOQOL-BREF were developed (WHOQOL Group, 1998).

The WHOQOL-BREF consists of 26 items, including two items on overall perceived quality of life and perceived health, and four domains: physical, psychological, social relationships, and environment. Each domain yields scores on a 20- or 100-point scale. The Turkish adaptation was performed by Eser et al. (1999).

8) Mini Mental State Examination (MMSE)

The Mini Mental State Examination was first published by Folstein and colleagues in 1975. The Turkish reliability and validity study was conducted by Güngen et al. (2002). The MMSE is a brief, widely used test to assess cognitive functioning. It is commonly used by clinicians for mental status examination and consists of five main components:

1. **Orientation in time and place:** The person is asked to provide the date, day, month, year, and season, as well as the name of the place, country, city, and building.
2. **Registration and short-term memory:** The examiner states three words and asks the person to repeat them; recall is assessed a few minutes later.
3. **Attention and calculation:** The person is asked to subtract serial sevens from 100 (e.g., 100, 93, 86, ...) or to spell a word backwards.
4. **Language and naming:** The person is asked to name several objects, to follow a simple command (e.g., "Take the paper and fold it in half"), and to read and understand a written sentence.
5. **Visuospatial skills:** The person is asked to copy a specific design or produce a simple drawing.

The MMSE is scored out of 30 points and is generally interpreted as follows: 24–30 = normal cognitive functioning; 19–23 = mild cognitive impairment; 10–18 = moderate impairment; 0–9 = severe impairment.

9) qEEG Recording

Resting-state qEEG recordings will be obtained in a quiet, dimly lit, air-conditioned room. A 19-channel qEEG cap (FP1, F7, T3, T5, F3, C3, P3, O1, Fz, Cz, Pz, F4, C4, P4, O2, FP2, F8, T4, T6) placed according to the international 10–20 system will be used. A transparent electrode gel will be injected into scalp electrodes to increase conductivity. The ground electrode will be placed at FPz. Mastoid electrodes will be attached to both earlobes as reference electrodes. Electrode impedance will be kept below 5 kΩ for all electrodes. Patients will sit comfortably with eyes closed in a resting state during recording. A Neuron-Spectrum-4/P device (Neurosoft, 2023) will be used. Total recording time will be approximately 7 minutes, consisting of 3 minutes of baseline recording, 30 seconds of eyes-open condition, and 3.5 minutes of eyes-closed condition. Data will be sampled at 500 Hz; the low-frequency filter will be set at 0.15 Hz, the high-frequency filter at 70 Hz, and a 50-Hz notch filter will be applied.

10) qEEG Analysis

Raw qEEG recordings will be saved in European Data Format (EDF). Offline muscle artifacts will be manually removed in NeuroGuide (Applied Neuroscience Inc., version 3.8.2) by an experienced qEEG reader. A 3-minute artifact-free segment will then be obtained. For each electrode, mean activity across the recording period will be calculated, and Fast Fourier

Transform (FFT) will be applied to compute spectral power in five main frequency bands: gamma (>35 Hz), beta (12–35 Hz), alpha (8–12 Hz), theta (4–8 Hz), and delta (0–4 Hz), including the following sub-bands: alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (12–15 Hz), beta2 (15–18 Hz), beta3 (18–25 Hz), gamma1 (30–35 Hz), and gamma2 (35–40 Hz). The calculated data will be saved as TDT files and exported to SPSS.

11) Event-Related Potential Measurement

Parameters of the P300 event-related potential will be assessed using an auditory oddball paradigm recorded with an EEG system (NeuronSpectrum-5, 2024). Recordings will take place in a sound-attenuated, semi-dark, well-ventilated room. A series of non-verbal auditory stimuli will be presented in random order, and participants will be instructed to press a button when they hear the target stimulus through headphones.

Stimuli will be delivered binaurally with a duration of 50 ms, intensity of 80 dB, and inter-stimulus interval of 1 s, at frequencies of 2000 Hz (target stimulus) and 1000 Hz (non-target stimulus). The number of target trials is expected to be approximately 25–30. Response amplitude and latency will be calculated as the peak-to-peak amplitude (μV) of the N250–P300 complex and the P300 latency (ms), respectively. P300 amplitude and latency will be measured using an EEG cap placed according to the 10–20 system with monopolar mastoid reference electrodes.

12) Measurement of REM Latency in Sleep EEG

Sleep Profiler (SP) recordings will be obtained from EEG sensor regions AF7–AF8, AF7–Fpz, and AF8–Fpz (Advanced Brain Monitoring, Carlsbad, CA, USA) applied by participants themselves at home. SP recordings will be automatically staged using machine-learning algorithms previously described in the literature, designed to comply with the standard visual scoring rules of the American Academy of Sleep Medicine. These AI-based staging algorithms combine epoch-level temporal power spectral features, automatically detected individual slow waves, sleep spindles, cortical arousals, EMG arousals, and epoch-level phasic correlations between two signals that contain electro-oculographic activity (AF7–Fpz versus AF8–Fpz).

The accuracy of automatic staging, with and without technical review, has been validated against visually scored PSG recordings, including in subjects referred for evaluation of sleep-disordered breathing. Sleep staging accuracy has also been validated against simultaneously acquired PSG recordings (Lewendowski et al., 2023).

13) Whole-Genome Sequencing

Whole-genome sequencing will be performed on genomic DNA isolated from peripheral blood samples. This approach yields the most comprehensive genetic data currently available.

Sequencing allows the detection of single nucleotide variations (SNVs), copy number variations (CNVs), insertions and deletions, haplotypes, gene fusions, and structural rearrangements. Whole-genome sequencing generates large amounts of data, which are analyzed using complex bioinformatic approaches. Common applications include undiagnosed diseases, population studies, pharmacogenetic research, and cancer research.

As technology advances, data quality increases, costs decrease, and bioinformatic analyses improve, leading to growing use worldwide. In our setting, genomic studies have been conducted using exome sequencing, which examines only protein-coding exons, to diagnose patients and to perform pharmacogenetic analyses of drug metabolism. Third-generation long-read sequencing, considered a new-generation technology, reveals all structural rearrangements and will allow us to perform both tissue compatibility analyses, which are very important in organ transplantation, and haplotype analyses for drug metabolism at lower cost and higher quality. Globally, technology is shifting in this direction.

14) Transcriptome Sequencing (RNA-Seq)

Transcriptome sequencing aims to identify all RNA molecules expressed in a given cell population at a specific time. Unlike DNA sequencing, RNA-Seq provides information about the dynamic properties of target cell populations.

RNA-Seq enables the examination of read counts for all expressed RNAs in the target cells, single nucleotide changes in expressed regions, insertions/deletions, fusion genes, and functional outcomes such as alternative splicing events caused by certain variants.

It is known that RNA profiles change in conditions such as disease, medication use, and infection. Therefore, RNA-Seq approaches are used to elucidate disease etiology, monitor treatment efficacy, and discover biomarkers.

15) Small RNA Sequencing

In addition to coding RNAs, the human genome contains short non-coding RNA molecules, including siRNA (small interfering RNA), miRNA (microRNA), snoRNA (small nucleolar RNA), and sncRNA (small non-coding RNA). These RNAs regulate various physiological and pathological processes within the cell. They control gene expression levels by degrading their target RNAs or by suppressing protein synthesis. Recent research has shown that small RNAs have great potential as biomarkers for the diagnosis and monitoring of diseases.

Small RNA studies, like transcriptome sequencing, rely on comparisons between groups and subsequent statistical analyses.

16) Long-Read Sequencing With PacBio: Methylation and Genotyping

Long-read whole-genome sequencing will be performed using Pacific Biosciences (PacBio) long-read technology. This platform generates high-fidelity (HiFi) long reads that enable comprehensive characterization of genomic variation and epigenetic regulation in a single experiment. PacBio long-read sequencing will be used to perform genome-wide genotyping, including single nucleotide variants (SNVs), insertions/deletions (indels), copy number variations (CNVs), and structural rearrangements, resolve haplotypes across clinically relevant loci, provide allele-specific information that is important for pharmacogenetic analyses and depression-related risk loci, simultaneously measure DNA methylation at single-base resolution.

Because PacBio sequencing measures the kinetics of DNA polymerase during sequencing, it can directly detect base modifications, including 5-methylcytosine (5mC), without the need for bisulfite conversion. In this study, we will use these data to obtain:

- Genome-wide DNA methylation profiles,
- CpG methylation patterns in genes and pathways previously associated with Major Depressive Disorder, stress response, and neuroplasticity,
- Allele-specific methylation in candidate regions that may influence treatment response and relapse risk.

Timepoint	**Clinical**	**EEG**	**P300**	**REM**	**MRI**	**RNA/Genome**
T0	✓	✓	✓	✓	✓	✓
T1 (4–8 wks)	✓	✓	✓	–	–	–
T2 (≥6 months remission)	✓	✓	✓	✓	–	✓
T3 (6 months drug-free)	✓	✓	✓	✓	✓	✓

Healthy controls receive **one full measurement** set.

8. Sample Size

The sample size calculation was performed using the **OpenEpi** web-based platform (OpenEpi – Sample Size for Unmatched Case-Control Studies, n.d.). OpenEpi is a free and open-source software widely used for epidemiological statistics. In the application, the module for **unmatched case–control studies** was selected.

Within this module, the desired confidence level (95% CI), statistical power (80%), an assumed exposure prevalence among controls (25%), and either an odds ratio of 1 or an assumed exposure prevalence among cases (50%) were entered.

Based on these parameters, the required sample size was calculated as **170 participants** using the Fleiss test with continuity correction.

An additional **20% dropout rate**, as reported in the literature (Pradier et al., 2020), was then added. Accordingly, the final required sample size was determined to be **204 participants**.

9. Ethical Considerations

- Study approved by Üsküdar University Non-interventional Ethics Committee (61351342/020-684-December 2024-33)
- Informed consent obtained.
- Non-interventional, observational design; medication decisions follow clinical guidelines.

10. Expected Results

1. **Relapsers vs Non-relapsers:**
   Significant differences in EEG, REM, P300, RNA/miRNA, MRI parameters.
2. **Healthy Comparison:**
   Relapsers will differ significantly from healthy at T2;
   Non-relapsers will *not differ* from healthy at T2.
3. **Clinical Utility:**
   Biomarkers that normalize → **safe antidepressant discontinuation**
   Biomarkers that do NOT normalize → **high relapse risk**, continue medication.

11. Impact and Significance

This study will provide the **first multimodal, longitudinally validated biological algorithm** for determining when antidepressant medication can be safely discontinued in MDD.

It proposes a shift from **symptom-based** to **biologically informed** treatment duration decisions.

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