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INVITED EDITORIAL

Sleep as a psychiatric vital sign, not just a symptom

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Every clinician who treats psychiatric illness knows that patients sleep badly. The usual assumption is that poor sleep is a consequence of the illness and will improve once the depression, mania, or psychosis is treated. Over the past three decades, work on the brain circuits that generate sleep, together with large clinical studies, has overturned that assumption (1). Disturbed sleep is not simply a by-product of psychiatric illness; it is often part of its cause and, unlike much of what we assess in psychiatry, it can be measured. We argue here that sleep deserves to be treated as a vital sign, recorded and acted upon as routinely as blood pressure.

HOW DOES THE BRAIN SWITCH BETWEEN SLEEP AND WAKING?

To see why sleep can serve as a vital sign, it helps to understand how the brain produces it. Sleep and wakefulness are not simply the brain slowing down and speeding up; they are two stable states, each actively generated, with rapid transitions between them (1, 2). On one side are the monoaminergic arousal cell groups that keep us awake: the noradrenergic locus coeruleus, the serotonergic raphe nuclei, and the histaminergic tuberomammillary nucleus. On the other are sleep-promoting neurons of the ventrolateral preoptic nucleus (VLPO) of the hypothalamus, which release the inhibitory transmitters γ -aminobutyric acid (GABA) and galanin. Each side inhibits the other, so the circuit behaves like an electrical flip-flop switch. It settles firmly into

waking or sleep and resists the drowsy middle ground (2). Orexin (also called hypocretin) neurons in the lateral hypothalamus act on the waking side of the switch and hold it steady; when they are lost, as in narcolepsy, the switch becomes unstable, and patients fall abruptly between states (3). That VLPO neurons are genuinely sleep-active was demonstrated directly when they were found to fire in step with sleep (4). Two points matter for psychiatry. First, this circuit produces outputs that can be counted: how quickly a patient falls asleep, how consolidated the night is, how the sleep stages are arranged, and when they occur. Second, the waking side of the switch is built from the very monoamine systems that psychiatry implicates in mood and anxiety and targets with its drugs. Thus, disturbances of sleep and mood are, in part, two views of the same circuitry.

IS THE SLEEP PROBLEM IN PSYCHIATRY ONLY INSOMNIA?

When psychiatrists speak of sleep, they usually mean insomnia. But insomnia is only the most visible part of a larger disturbance. When sleep is recorded overnight, patients across a range of psychiatric diagnoses show changes in its architecture, with reduced continuity and efficiency and shifts in the amount and timing of slow-wave and rapid-eye-movement (REM) sleep; few disorders leave sleep entirely normal (5). In major depression, the oldest and best-established findings are that REM sleep begins too early in the night and becomes too

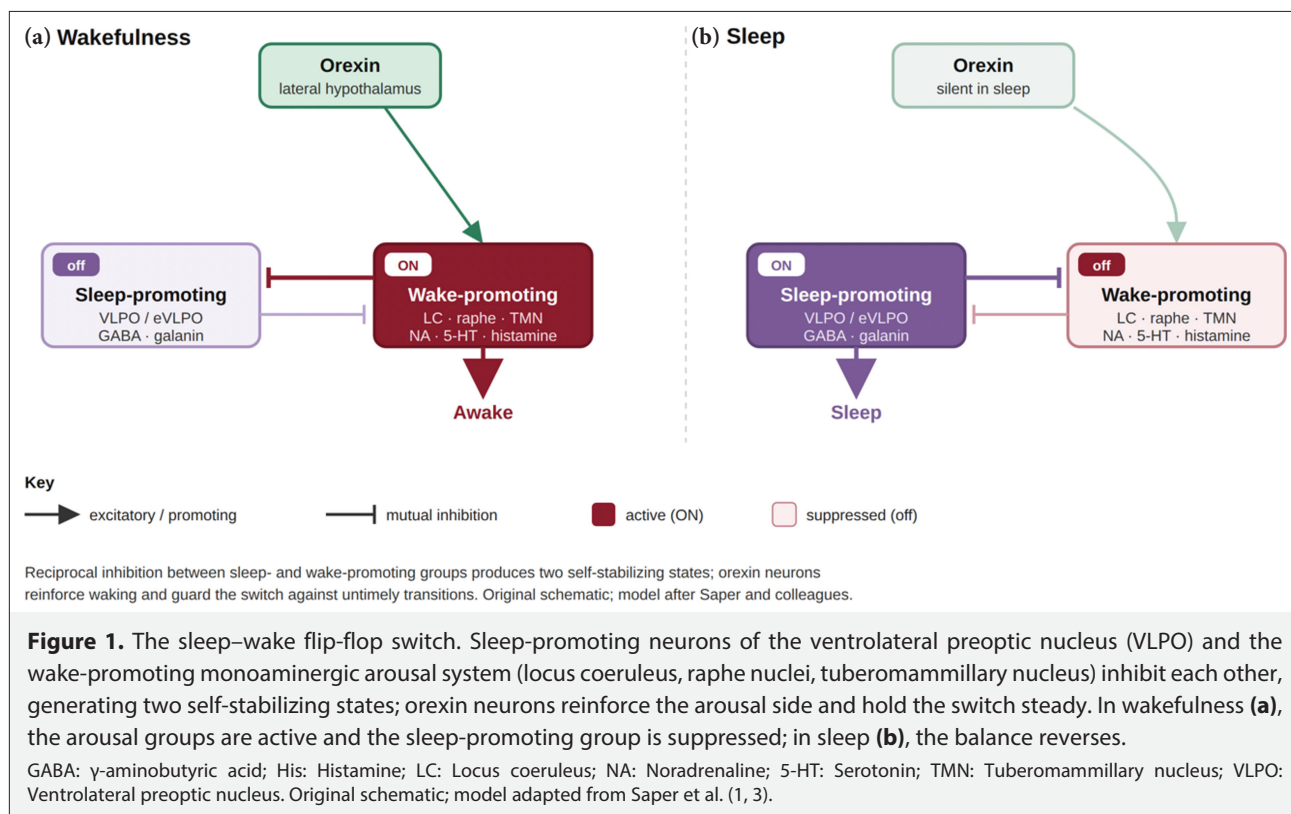
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intense, while deep slow-wave sleep is reduced (6). These are not complaints; they are measurable features of the night.

The disturbance reaches down to the fine structure of sleep as well. Sleep spindles, the brief bursts of oscillation generated by the thalamus during non-REM sleep, are strikingly reduced in schizophrenia, both in patients who have never taken medication and in those who have, and, to a lesser degree, in their unaffected relatives (7). The magnitude of the spindle deficit tracks how poorly patients consolidate memories overnight, making spindles both a candidate biomarker and a potential treatment target (8). Schizophrenia also disturbs the timing of sleep, producing a misalignment of the sleep-wake cycle that persists even when medication and daytime inactivity are taken into account (9). Sleep pathology in psychiatry is therefore both coarse- and fine-grained, and it carries information that a single question about difficulty sleeping cannot capture.

DOES POOR SLEEP COME BEFORE THE ILLNESS?

If disturbed sleep were only a symptom, it would arrive with the illness and leave with it. Often, it does neither. Sleep disturbance cuts across diagnostic

boundaries, recurring in mood, anxiety, psychotic, and substance use disorders and sharing mechanisms with them, which has led to its description as a transdiagnostic process rather than a symptom of any one disease (10). Its timing is more telling still. In long-term studies, insomnia roughly doubles the chance that a person will later experience a first episode of depression (11), and it also forecasts the later appearance of anxiety, psychosis, and substance use disorders (12). In many patients, the sleep problem appears before the rest of the illness and lingers between episodes, behaving less like a passenger and more like an early, and often modifiable, part of the disorder (13).

DOES SLEEP CAUSE THE TROUBLE, OR ONLY REFLECT IT?

Prediction is not proof of cause, and sleep and mood plainly influence each other. Two lines of evidence, however, point to sleep as a genuine contributor. The first comes from genetics. Mendelian-randomization studies use inherited variants as natural experiments that approximate the random assignment of a trial and reduce the influence of confounding and reverse causation; these analyses suggest that insomnia contributes to depression and related conditions, and

not merely the reverse (14). The second comes from treatment. In the largest trial of its kind, improving sleep in people with insomnia reduced paranoia and hallucinations, and the analysis showed that the benefit was mediated by the improvement in sleep itself (15). Adding treatment for insomnia to the treatment of depression also improves depressive symptoms beyond treating mood alone (16). In the same vein, poor sleep is associated with the occurrence and severity of delusions and hallucinations and often precedes relapse in psychosis (17). Even a single sleepless night weakens the control that the prefrontal cortex normally exerts over the amygdala, demonstrating in the laboratory how lost sleep can unsettle emotional regulation (18).

WHAT SHOULD THE CLINICIAN DO?

The practical message is simple. Sleep should be asked about and documented at every psychiatric visit (its duration, continuity, timing, and the patient's natural rhythm) as routinely as we record blood pressure. A sleep diary and a brief questionnaire such as the Insomnia Severity Index take little time and provide a number that can be followed over weeks (19); actigraphy and, increasingly, validated wearable devices bring objective measurement within reach. When sleep is abnormal, it should be treated in its own right rather than set aside until the main diagnosis improves. Cognitive behavioral therapy for insomnia is now recommended as first-line treatment for chronic insomnia (20). Attention to circadian timing, through scheduled light exposure and a regular sleep–wake pattern, addresses the clock; when medication is needed, drugs aimed at the arousal system, such as dual orexin-receptor antagonists, may suit the problem better than general sedation (21). Because sleep and psychiatric illness feed one another, improvement in either tends to help the other.

WHY DOES THIS MATTER BEYOND PSYCHIATRY?

There is a final reason to take sleep seriously. Sleep does more than rest the mind; during deep non-REM sleep, the brain clears metabolic waste more efficiently than during wakefulness (22). This finding links chronic sleep loss to neurodegenerative and other medical diseases and reminds us that broken sleep is seldom harmless in any illness. Clinicians already ask

their patients whether they sleep. What is usually missing is the habit of measuring the answer, attending to its detail, and acting on it. To treat sleep as a vital sign (something to be measured, followed, and corrected rather than noted and excused) would be a small change in practice with potentially large returns. Making it real will require simple measurement standards, a place for sleep in the medical record, and trials that ask whether treating sleep to a target improves the outcomes of psychiatric illness.

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RESEARCH ARTICLE

Characteristics and outcomes of early-terminated acute electroconvulsive therapy courses: A retrospective cohort study

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ABSTRACT

Objective: Acute electroconvulsive therapy (ECT) courses may end early because of rapid clinical improvement or interruption by an adverse event. However, the determinants of early termination and the subsequent clinical course remain poorly characterized. This study examined factors associated with the number of sessions in early-terminated ECT courses and their clinical outcomes.

Method: We reviewed the records of adult psychiatric inpatients who received five or fewer bifrontal ECT sessions at a tertiary center between 2019 and 2023. After excluding non-clinical discharges, 523 patients were categorized into those receiving three or fewer sessions (n=136) and those receiving four to five sessions (n=387). Groups were compared on clinical, anesthetic, and outcome variables. Adjusted analyses and analyses stratified by diagnosis and American Society of Anesthesiologists (ASA) physical status examined the independence of the session-group effect, and missing clinical severity ratings were imputed.

Results: The groups did not differ in age, diagnosis, baseline illness severity, ASA physical status, or anesthetic parameters. Adverse-event-related termination occurred in 73.5% of patients receiving three or fewer sessions compared with 14.5% of those receiving four to five sessions, whereas rapid clinical response accounted for 85.0% of terminations in the latter group (p<0.001). After adjustment, receiving three or fewer sessions was associated with a sixteenfold increase in the odds of adverse-event-related termination (adjusted odds ratio: 16.18, 95% confidence interval [CI]: 9.70–26.97), independent of diagnosis and ASA status. Illness severity at ECT termination was greater in the ≤3-session group (d=1.43–1.76), but severity at hospital discharge did not differ between groups.

Conclusion: Among early-terminated ECT courses, session number primarily reflects whether treatment ended because of rapid clinical response or an adverse event, with adverse-event-related termination concentrated among the shortest courses, independent of diagnosis and medical risk. The absence of differences in clinical status at discharge suggests that, when appropriately managed, early termination due to adverse events is compatible with favorable short-term outcomes.

Keywords: Electroconvulsive therapy, treatment outcome, treatment discontinuation, psychotic disorders, bipolar disorder

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INTRODUCTION

Electroconvulsive therapy (ECT) remains one of the most effective treatments in psychiatry and continues to play a central role in managing severe mental disorders when rapid symptom control is required or when pharmacological treatments have failed (1-4). Its efficacy is well established across diagnostic categories. Meta-analyses report response rates of approximately 74% in unipolar depression and 77% in bipolar depression, with comparable remission rates and more rapid response among patients with bipolar disorder (5, 6). A decade-long national study from Scotland found response and remission rates of 73% and 51%, respectively, in patients with moderate-to-severe depressive illness (7). In schizophrenia spectrum disorders, reported remission rates range from 40% to 80%, although these patients generally require longer treatment courses (8).

The therapeutic effects of ECT emerge rapidly and are concentrated during the early phase of treatment. In the Consortium for Research in ECT cohort, more than half of responders showed an initial response by the third session, and approximately one-third achieved remission by the sixth treatment (9, 10). The first ECT session alone accounts for a substantial proportion of the overall symptomatic improvement observed during an acute course (11). In routine clinical practice, decisions to continue or discontinue ECT are largely guided by clinical response, with treatment typically ending once remission is achieved or further improvement plateaus. Consequently, the number of sessions a patient receives generally reflects the speed and completeness of therapeutic response: patients who improve rapidly require fewer treatments, whereas those with slower or incomplete improvement receive longer courses (12).

Clinical response, however, explains only part of the variation in treatment duration. Some acute ECT courses are terminated before the intended clinical endpoint because medical or neurological complications make further treatment inadvisable. Common complications include postictal confusion or agitation, transient cognitive impairment, and peri-procedural cardiovascular or respiratory events (13-15). Postictal agitation has been reported in 8%–65% of patients, depending on the definition and study population, while a systematic review involving more than 100,000 patients estimated that major adverse cardiac events occur in approximately one of every 50 patients undergoing ECT (16, 17). Although most

adverse events are transient and manageable, they may necessitate interruption or premature termination of treatment (18). Unlike treatment response, these events are not strongly associated with psychiatric diagnosis or baseline symptom severity but are more closely related to seizure characteristics, anesthetic factors, advanced age, and pre-existing medical comorbidity, particularly cardiovascular disease (19, 20). Consistent with this observation, a large registry study of the oldest-old found that neither medical comorbidity nor ECT treatment parameters predicted clinical outcome (21).

Despite the clinical importance of completing an acute ECT course, relatively little is known about the factors leading to early termination. Most studies have focused on treatment efficacy, remission, or cognitive outcomes, whereas the reasons why acute ECT courses end, and how these relate to the number of treatments received, have received comparatively little attention (22, 23). National audit data suggest that most courses are completed as planned and that discontinuation because of adverse events is uncommon. However, published cohorts rarely distinguish systematically between response-driven and adverse-event-driven termination or examine whether patients whose treatment ends prematurely because of complications nevertheless achieve satisfactory clinical outcomes by hospital discharge (24). Addressing this question is clinically important because it determines whether early termination should be viewed as treatment failure or as a manageable interruption that does not necessarily compromise short-term recovery.

The present study addresses this gap by examining a well-defined cohort of psychiatric inpatients whose acute ECT course ended after five or fewer sessions. Within this cohort, patients were grouped according to treatment exposure and compared across demographic, clinical, anesthetic, and outcome measures. The study had three objectives: (1) to identify the clinical factors associated with the number of ECT sessions received; (2) to determine whether the reasons for treatment termination, particularly adverse-event-related cessation, differed by session number independently of psychiatric diagnosis and medical risk; and (3) to evaluate whether differences in clinical status at the end of ECT persisted until hospital discharge.

METHODS

Study Design and Setting

This retrospective observational study was conducted at a specialized tertiary psychiatric center in Türkiye.

Data were obtained from routinely collected clinical records of patients who received ECT between January 2019 and December 2023. No experimental interventions were introduced, and all procedures reflected standard institutional clinical practice. Patient anonymity and data confidentiality were maintained throughout the study. The study was approved by the institutional clinical research ethics committee (Protocol No. 2026/197), which waived the requirement for individual informed consent because of the retrospective study design. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Participants

The study population comprised adults (≥ 18 years) who received ECT and completed five or fewer sessions during the study period. This threshold operationalized early treatment termination, defined as discontinuation of an acute ECT course before completion of the minimum six sessions recommended by major clinical guidelines for therapeutically adequate treatment exposure (1, 2).

Patients were excluded if they were younger than 18 years; received more than five ECT sessions or completed a planned acute course; had missing or unverifiable information regarding the number of sessions; or had incomplete core clinical data. Patients whose hospitalization ended through discharge against medical advice, early release to family before clinical completion, or inter-facility transfer were also excluded because these non-clinical exits reflected administrative or family-initiated decisions rather than clinician-directed treatment cessation and could therefore confound analyses of clinically determined termination patterns. One patient was excluded because of an implausible height value attributed to a data-entry error. The final analytic sample comprised 523 patients (≤ 3 sessions, $n=136$; 4–5 sessions: $n=387$).

Measures

Data were extracted systematically using a structured abstraction framework. Sociodemographic variables included age, sex, marital status, years of education, and substance use history (present/absent). Psychiatric diagnoses were grouped into four categories: schizophrenia spectrum disorders, bipolar disorder, depressive disorders, and other psychotic disorders (including substance-induced psychosis and other psychotic diagnoses). Medical status was assessed using the American Society of Anesthesiologists (ASA) Physical Status Classification and dichotomized

as ASA I versus ASA II–III to distinguish lower from higher medical risk (25). Procedural variables included propofol dose, suxamethonium dose, and serum pseudocholinesterase activity, the latter measured because deficiency prolongs suxamethonium-induced neuromuscular blockade. Peri-procedural systolic and diastolic blood pressure, heart rate, body temperature, and oxygen saturation were recorded immediately before and after each ECT session. Delta scores were calculated as post-procedure minus pre-procedure values. Clinical severity was assessed using the Clinical Global Impression–Severity scale (CGI-S; range 1–7) at baseline, at completion of the ECT course, and at hospital discharge (26).

Grouping Variable and Outcome Definitions

Patients were categorized into those receiving three or fewer sessions and those receiving four to five sessions, representing a clinically meaningful gradient of treatment exposure within the early-termination cohort. This grouping was defined a priori based on the observed distribution of session counts. The primary outcome was the reason for ECT termination, categorized as early clinical response, adverse effect or medical complication, patient- or family-initiated discontinuation, or insufficient response/other. A binary outcome variable, adverse-event-related termination, identified patients whose ECT course ended because of a documented treatment-emergent adverse event or medical complication. This patient-level indicator reflects whether treatment was terminated because of an adverse event but does not quantify the number of events or capture adverse events that did not result in treatment discontinuation. Secondary outcomes included CGI-S at ECT termination and hospital discharge, change in CGI-S from baseline to ECT termination (CGI delta), and hospital course variables.

ECT Procedure

All ECT sessions were administered under general anesthesia with neuromuscular blockade according to established clinical guidelines (1, 2) and institutional protocols (14). Bifrontal ECT was delivered using a Thymatron IV brief-pulse device. Electrode placement and initial stimulus intensity were determined using the half-age method, a commonly employed titration approach in which the initial stimulus energy, expressed as a percentage of the device output, is set to approximately half the patient's age (e.g., 20% for a 40-year-old patient). When seizure duration was shorter than 25 seconds, stimulus intensity

was increased according to institutional guidelines. Decisions regarding continuation or termination of treatment were made within routine multidisciplinary clinical practice.

Statistical Analysis

Normality was assessed using skewness and kurtosis coefficients (27). Normally distributed continuous variables were compared using Welch's *t* test and summarized with Cohen's *d*. Non-normally distributed continuous and ordinal variables were analyzed using the Mann–Whitney *U* test with rank-biserial *r*, whereas categorical variables were compared using Pearson's chi-square test with Cramér's *V*. Fisher's exact test was used when expected cell counts were fewer than five. Effect sizes were interpreted according to Cohen's guidelines (28). End-of-ECT and discharge CGI-S scores were missing in 37.2% and 38.7% of patients, respectively. Missingness occurred almost exclusively among patients whose treatment ended because of early clinical response (62.6% missing in this subgroup versus $\leq 0.6\%$ in all other groups), consistent with a missing-at-random mechanism conditional on termination reason. Missing values were imputed using multiple imputation by chained equations (MICE) with random forest models (20 datasets, 10 iterations), and estimates were pooled using Rubin's rules (29). Complete-case analyses are performed as a sensitivity analysis. To evaluate whether session-group effects were independent of diagnosis and medical risk, analysis of covariance (ANCOVA) was used to examine CGI delta, and logistic regression was used to examine adverse-event-related termination. Both models adjusted for diagnosis, ASA risk group, suxamethonium dose, and pseudocholinesterase activity, with additional stratified analyses by diagnosis and ASA subgroup. Age and sex were not included in adjusted models. Sex was associated with session-group assignment, introducing collinearity with the primary predictor, whereas age was considered to be adequately represented by ASA physical status. All statistical tests were two-sided with a significance level of $\alpha=0.05$. Analyses were conducted using Python 3.12 (SciPy, pandas, statsmodels, and miceforest). No generative artificial intelligence tools were used to generate study data or results.

RESULTS

Sample Characteristics

The final analytic sample comprised 523 patients, including 136 (26.0%) in the ≤ 3 -session group and

387 (74.0%) in the 4–5-session group. Baseline demographic and clinical characteristics are summarized in Table 1. The groups did not differ in age, years of education, body weight, marital status, smoking, alcohol use, or substance use (all $p \geq 0.064$). However, males were more common in the ≤ 3 -session group than in the 4–5-session group (57.4% vs. 42.4%; $\chi^2[1]=8.49$, $p=0.004$, $V=0.127$). Diagnostic distribution was similar between groups ($\chi^2[4]=6.64$, $p=0.084$). Schizophrenia spectrum disorders predominated in the ≤ 3 -session group (43.8%), whereas diagnoses were more evenly distributed among patients receiving four to five sessions. ECT indication also did not differ significantly ($p=0.116$), nor did the proportion of patients classified as ASA II–III (72.8% vs. 70.0%; $p=0.068$). Baseline CGI-S scores were equivalent between groups (both median=2.0; $p=0.737$).

Anesthetic parameters were likewise comparable, including propofol dose ($p=0.218$), suxamethonium dose ($p=0.064$), and pseudocholinesterase activity ($p=0.605$). No between-group differences were observed in peri-procedural hemodynamic measures before or after treatment or in corresponding delta values (all $p \geq 0.194$), indicating similar cardiovascular and respiratory responses to ECT. Postictal orientation scores were also comparable ($p=0.737$). Total length of hospitalization ($p=0.905$) and the interval from admission to the first ECT session ($p=0.159$) did not differ between groups. However, patients receiving three or fewer sessions remained hospitalized significantly longer after their final ECT treatment (median, 10.0 vs. 5.0 days; $U=33.418$, $p<0.001$, $r_K=-0.299$).

CGI-S Outcomes

CGI-S outcomes are presented in Table 2. In the complete-case analysis, patients receiving three or fewer ECT sessions had significantly higher CGI-S scores at ECT termination (mean 3.69 ± 0.50) than those receiving four to five sessions (2.95 ± 0.53 ; $t[294]=12.33$, $p<0.001$, $d=1.43$). They also exhibited significantly greater CGI delta ($d=0.97$), indicating substantially less clinical improvement—or greater clinical deterioration—at treatment termination. Despite these differences, CGI-S scores at hospital discharge did not differ between groups ($d=0.02$, $p=0.897$), indicating convergence of clinical status before discharge.

Missing end-of-ECT CGI-S values were concentrated almost entirely among early responders in the 4–5-session group. Imputed values reflected

Table 1: Demographic and clinical characteristics according to ECT session group (n=523)

Characteristic	≤3 sessions (n=136)	4–5 sessions (n=387)	Test	p	Effect size
Continuous variables					
Age (years), M (SD)	39.65 (12.78)	39.91 (13.03)	t(521)=−0.20	0.839	d=−0.02
Education (years), M (SD)	7.09 (3.69)	6.96 (3.64)	t(521)=0.35	0.724	d=0.04
Body weight (kg), M (SD)	76.74 (20.82)	73.86 (16.75)	t(521)=1.46	0.147	d=0.16
Propofol dose (mg), M (SD)	65.51 (17.77)	63.41 (15.03)	t(521)=1.23	0.218	d=0.13
Pseudocholinesterase (U/L), M (SD)	8.379 (2.493)	8.254 (2.186)	t(521)=0.52	0.605	d=0.06
Hospital stay (days), M (SD)	25.10 (14.48)	24.94 (10.91)	t(514)=0.12	0.905	d=0.01
Time from last ECT to discharge, Mdn [IQR]	10.0 [4.0–17.0]	5.0 [1.0–10.0]	U=33.418	<0.001	r _K =−0.30
Baseline CGI-S, Mdn [IQR]	2.0 [2.0–3.0]	2.0 [2.0–3.0]	U=26.751	0.737	r _K =−0.02
Categorical variables					
Male sex, n (%)	78 (57.4)	164 (42.4)	χ ² (1)=8.49	0.004	V=0.13
Single marital status, n (%)	85 (62.5)	234 (60.5)	χ ² (1)=0.10	0.752	V=0.01
Current smoking, n (%)	87 (64.0)	236 (61.0)	χ ² (1)=0.26	0.607	V=0.02
Substance use, n (%)	32 (23.5)	73 (18.9)	χ ² (1)=1.09	0.296	V=0.05
Diagnosis, n (%) ^a			χ ² (3)=6.64	0.084	V=0.12
Schizophrenia spectrum disorders	56 (43.8)	119 (32.6)			
Bipolar disorder	29 (22.7)	116 (31.8)			
Depressive disorders	32 (25.0)	89 (24.4)			
Other psychotic disorders	11 (8.6)	41 (11.2)			
ASA physical status II–III, n (%)	99 (72.8)	271 (70.0)	χ ² (1)=3.34	0.068	V=0.08

M: Mean; SD: Standard deviation; Mdn: Median; IQR: Interquartile range; CGI-S: Clinical Global Impression–Severity; ASA: American Society of Anesthesiologists physical status classification. Continuous variables were compared using Welch's t test (Cohen d), ordinal variables using the Mann–Whitney U test (rank-biserial r_K), and categorical variables using the chi-square test (Cramér's V). ^an=128/365; after excluding cases with missing data.

Table 2: Clinical Global Impression–Severity (CGI-S) outcomes according to ECT session group: complete-case and multiple imputation (MICE) analyses (n=523)

Outcome	≤3 sessions M (SD)	4–5 sessions M (SD)	t	p	d	Analysis
End-of-ECT CGI-S	3.69 (0.50)	2.95 (0.53)	12.33	<0.001	1.43	Complete-case
End-of-ECT CGI-S	3.69 (0.50)	2.81 (0.50)	17.54 ^a	<0.001	1.76	MICE
Discharge CGI-S	2.42 (0.54)	2.41 (0.51)	0.13	0.897	0.02	Complete-case
Discharge CGI-S	2.43 (0.55)	2.42 (0.50)	0.33 ^a	0.745	0.03	MICE
Change in CGI-S (end of ECT – baseline)	1.25 (0.80)	0.57 (0.61)	8.12	<0.001	0.97	Complete-case
Change in CGI-S (end of ECT – baseline)	1.24 (0.81)	0.41 (0.56)	11.13 ^a	<0.001	1.32	MICE

CGI-S: Clinical Global Impression–Severity (range 1–7). Change in CGI-S was calculated as the end-of-ECT score minus the baseline score. Complete-case analyses included n=135/161 patients for end-of-ECT CGI-S and n=134/153 for discharge CGI-S. MICE: m=20 datasets; Rubin's rules (n=523). Effect size: Cohen's d. ^aPooled t statistic calculated using the Barnard–Rubin method. SD: Standard deviation; ECT: Electroconvulsive therapy; CGI-S: Clinical Global Impression–Severity; MICE: Multiple imputation by chained equation.

this distribution (71.6% CGI-S=3, 28.4% CGI-S=2). Following multiple imputation, the mean end-of-ECT CGI-S score for the 4–5-session group decreased from 2.95 to 2.81, increasing the between-group effect size (d=1.76). The comparison at discharge remained non-significant (d=0.03, p=0.745), confirming the robustness of the null finding.

ECT Cessation Patterns

ECT cessation characteristics are summarized in Table 3a. Both termination type and termination reason differed markedly between groups, with large effect sizes. Disease- or adverse-event-related termination occurred in 66.9% of patients receiving three or fewer sessions compared with 14.2% of those receiving four

Table 3a: ECT termination characteristics according to session group (n=523)

Characteristic	≤3 sessions (n=136) n (%)	4–5 sessions (n=387) n (%)	χ^2 (df)	p; Effect size
Termination type			$\chi^2(3)=225.05$	<0.001 ; V=0.66
Remission	1 (0.7)	162 (41.9)		
Partial remission	23 (16.9)	168 (43.4)		
Natural termination	21 (15.4)	2 (0.5)		
Disease- or adverse-event-related termination	91 (66.9)	55 (14.2)		
Termination reason			$\chi^2(3)=181.84$	<0.001 ; V=0.59
Early clinical response	31 (22.8)	329 (85.0)		
Adverse event or medical complication	100 (73.5)	56 (14.5)		
Patient- or family-initiated discontinuation	3 (2.2)	1 (0.3)		
Insufficient response/other	2 (1.5)	1 (0.3)		
Adverse-event-related termination	100 (73.5)	56 (14.5)	$\chi^2(1)=164.89$	<0.001 ; V=0.56

ECT: Electroconvulsive therapy; V: Cramér's V. Patients with non-clinical discharges were excluded from the analytic sample (see Participants); therefore, unauthorized discharge is not represented. Adverse-event-related termination is a binary outcome derived from the documented reason for ECT cessation.

Table 3b: Medical complications leading to adverse-event-related ECT termination (n=523)

Variables	≤3 sessions (n=136) n (%)	4–5 sessions (n=387) n (%)	χ^2 (df)	p; Effect size
Medical complication, n (%)	100 (73.5)	56 (14.5)	$\chi^2(1)=164.89$	<0.001 ; V=0.56
Postictal confusion	11 (11.0)	32 (57.0)		
Cardiovascular instability	27 (27.0)	6 (10.0)		
Infection	15 (15.0)	5 (9.0)		
Bronchoconstriction	25 (25.0)	4 (7.0)		
Other complications	22 (25.0)	9 (17.0)		

ECT: Electroconvulsive therapy. Cardiovascular instability included tachycardia, bradycardia, hypertension, and hypotension. Other complications included agitation, headache, hypersalivation, and rash/flushing.

to five sessions, whereas remission or partial remission accounted for 85.3% of terminations in the latter group ($\chi^2[3]=225.05$, $p<0.001$, $V=0.656$). Analysis of specific termination reasons showed an even stronger contrast. Among patients receiving three or fewer sessions, 73.5% discontinued because of an adverse effect or medical complication and 22.8% because of early clinical response. In contrast, among patients receiving four to five sessions, 85.0% discontinued because of early response and only 14.5% because of adverse events ($\chi^2[3]=181.84$, $p<0.001$, $V=0.590$). Insufficient therapeutic response accounted for fewer than 2% of terminations in either group, indicating that differences between groups were not explained by treatment efficacy. The binary adverse-event-related termination outcome confirmed this marked contrast (73.5% vs. 14.5%; $\chi^2[1]=164.89$, $p<0.001$, $V=0.561$). The specific medical conditions leading to treatment discontinuation are summarized in Table 3b. Among patients receiving three or fewer sessions, cardiovascular

instability (tachycardia, bradycardia, hypertension, or hypotension) was the most common reason for discontinuation (27%), followed by bronchoconstriction (25%). In contrast, among patients receiving four to five sessions, postictal confusion was the leading cause of adverse-event-related termination (57%).

Adjusted and Stratified Analyses

Results of the adjusted analyses are presented in Tables 4a and 4b. In the analysis of covariance (ANCOVA), session group was the strongest predictor of CGI delta ($B=-0.798$, 95% confidence interval [CI]: -0.927 to -0.670, $p<0.001$), indicating approximately 0.80 additional CGI-S units of worsening (or reduced improvement) among patients receiving three or fewer sessions after adjustment for diagnosis, ASA status, and anesthetic variables. No diagnostic category differed from the schizophrenia spectrum reference group (all $p\geq 0.312$), indicating that the

Table 4a: Adjusted analysis of change in Clinical Global Impression–Severity (CGI-S): analysis of covariance (ANCOVA)

Predictor	B or aOR	95% CI	p
ANCOVA — CGI delta (MICE, m=20)			
≤3 vs. 4–5 sessions (main effect)	-0.798	[-0.927, -0.670]	<0.001
Bipolar disorder vs. schizophrenia spectrum disorders	+0.022	[-0.118, +0.161]	0.761
Depressive disorders vs. schizophrenia spectrum disorders	-0.076	[-0.222, +0.071]	0.312
Other psychotic disorders vs. schizophrenia spectrum disorders	+0.002	[-0.196, +0.199]	0.985
Suxamethonium dose (per mg)	<0.001	[-0.006, +0.007]	0.892
Pseudocholinesterase (per U/L)	<0.001	—	0.045

ANCOVA: Analysis of covariance; B: Unstandardized coefficient. Reference categories: 4–5 sessions, schizophrenia spectrum disorders, and ASA physical status I. Age and sex were excluded from the model (see Method). MICE: Multiple imputation by chained equations (m=20; Rubin's rules). aOR: Adjusted odds ratio; CI: Confidence interval.

Table 4b: Logistic regression for adverse-event-related termination

Predictor	B or aOR	95% CI	p
Logistic regression model — adverse-event-related termination (n=466)			
≤3 vs. 4–5 sessions	16.18	[9.70, 26.97]	<0.001
ASA II–III vs. ASA I	1.39	[0.79, 2.45]	0.254
Suxamethonium dose (per mg)	1.00	[0.97, 1.03]	0.962
Pseudocholinesterase (per U/L)	1.00	[1.00, 1.00]	0.513
Nagelkerke R ²	0.264	—	—

Logistic regression: B: unstandardized coefficient. Reference categories were 4–5 sessions and ASA physical status I. aOR: Adjusted odds ratio; N=466 after listwise deletion for missing suxamethonium dose. Age and sex were excluded from the model (see Method). MICE: Multiple imputation by chained equations (m=20; Rubin's rules). CI: Confidence interval; ASA: American Society of Anesthesiologists.

Table 5: Stratified change in CGI-S according to diagnosis and ASA physical status: ≤3 versus 4–5 ECT sessions (MICE-pooled estimates)

Diagnosis ASA physical status	≤3 sessions (n)	4–5 session (n)	p	Note
Schizophrenia spectrum disorders ASA I	1.31 (13)	0.38 (43)	<0.001	
Schizophrenia spectrum disorders ASA II–III	1.19 (43)	0.42 (76)	<0.001	
Bipolar disorder ASA II–III	1.33 (21)	0.41 (77)	<0.001	
Depressive disorders ASA I	1.25 (4)	0.42 (19)	0.094	n ₁ <10
Depressive disorders ASA II–III	0.96 (28)	0.38 (70)	0.001	
Other psychotic disorders ASA II–III	1.56 (9)	0.49 (30)	<0.001	n ₁ <10

Values are MICE-pooled mean change in CGI-S, calculated as end-of-ECT minus baseline. ASA: American Society of Anesthesiologists physical status classification. Between-group comparisons were performed using the Mann–Whitney U test. Strata with fewer than 10 patients in the ≤3-session group should be interpreted with caution. ECT: Electroconvulsive therapy.

session-group effect was not moderated by diagnosis. Pseudocholinesterase activity showed a statistically significant but clinically negligible association ($p=0.045$; $B<0.001$), whereas suxamethonium dose was not associated with CGI delta ($p=0.892$). In the logistic regression model, patients receiving three or fewer sessions had a sixteenfold increase in the adjusted odds of adverse-event-related termination (adjusted odds ratio [aOR]=16.18, 95% CI: 9.70 to 26.97, $p<0.001$). ASA risk group (aOR=1.39, $p=0.254$), suxamethonium dose, and pseudocholinesterase activity were not significant predictors. The model explained 26.4% of the variance (Nagelkerke $R^2=0.264$).

Stratified analyses (Tables 5 and 6) demonstrated that the session-group effect was consistent across diagnostic and ASA subgroups. Stratified analyses of CGI-S change were significant in all adequately powered strata (Table 5), with the ≤3-session group showing greater worsening (or less improvement) across schizophrenia spectrum disorders, bipolar disorder, and depressive disorders, as well as across both ASA physical status categories. Likewise, stratified rates of adverse-event-related termination (Table 6) ranged from 67% to 75% in the ≤3-session group and from 6% to 18% in the 4–5-session group across all adequately powered strata. This pattern persisted across diagnostic

Table 6: Stratified rates of adverse-event-related termination according to diagnosis and ASA physical status: ≤ 3 versus 4–5 ECT sessions

Diagnosis ASA physical status	≤ 3 sessions (n)	4–5 sessions (n)	p	Note
Schizophrenia spectrum disorders ASA I	69% (13)	14% (43)	<0.001	
Schizophrenia spectrum disorders ASA II–III	73% (41)	18% (68)	<0.001	
Bipolar disorder ASA I	75% (8)	6% (36)	<0.001	$n_1 < 10$
Bipolar disorder ASA II–III	71% (21)	18% (74)	<0.001	
Depressive disorders ASA I	75% (4)	16% (19)	0.068	$n_1 < 10$
Depressive disorders ASA II–III	73% (26)	12% (67)	<0.001	
Other psychotic disorders ASA II–III	67% (9)	8% (26)	0.002	$n_1 < 10$

Values are the percentage of patients with adverse-event-related termination. ASA: American Society of Anesthesiologists physical status classification. Between-group comparisons were performed using the chi-square test. Strata with fewer than 10 patients in the ≤ 3 -session group should be interpreted with caution. ECT: Electroconvulsive therapy.

groups and ASA physical status categories, supporting the independence of the observed association from psychiatric diagnosis and medical comorbidity. Results from strata containing fewer than 10 patients in the ≤ 3 -session group are reported for completeness but should be interpreted cautiously.

DISCUSSION

In this retrospective cohort of 523 psychiatric inpatients whose acute ECT courses ended after five or fewer sessions, the number of sessions received was associated with a distinct and clinically coherent pattern. The ≤ 3 -session and 4–5-session groups did not differ in age, education, body weight, diagnostic distribution, ECT indication, baseline severity, anesthetic parameters, hemodynamic responses, or postictal orientation. Instead, the groups differed primarily in why treatment ended. Nearly three-quarters of courses in the ≤ 3 -session group were terminated because of an adverse effect or medical complication, whereas most courses in the 4–5-session group ended because of early clinical response. After adjustment for diagnosis, medical risk, and anesthetic parameters, receiving three or fewer sessions was associated with a sixteenfold increase in the odds of adverse-event-related termination. Despite a large difference in clinical severity at ECT cessation, the groups had com-parable severity at hospital discharge.

The principal finding—that session number within an early-terminated course primarily reflects whether treatment ended because of clinical improvement or an adverse event—is consistent with the established clinical course of acute ECT. Because therapeutic response is often rapid and concentrated in the early phase of treatment (9–11), patients who improve quickly may require relatively few sessions before

treatment is concluded on clinical grounds. The 4–5-session group closely followed this pattern, with early response accounting for 85% of terminations. By contrast, the ≤ 3 -session group represented a different clinical pathway, in which treatment was interrupted by medical or neurological complications before a longer course could be delivered. The finding that insufficient response accounted for fewer than 2% of terminations in either group is also informative: early cessation generally reflected either rapid benefit or treatment intolerance rather than therapeutic failure. This is consistent with clinical practice, in which inadequate response typically leads to continuation or modification of treatment rather than immediate discontinuation (30).

The operational definitions of early termination and early clinical response, as well as the distinction between ≤ 3 sessions and 4–5 sessions, warrant clarification. Early termination was defined as discontinuation of an acute ECT course before completion of six sessions, the minimum treatment exposure generally recommended by major clinical guidelines for an adequate therapeutic trial. Within this cohort, treatment cessation was further classified according to its primary underlying reason: interruption because of an adverse event or other non-response-related factor versus planned termination following achievement of a clinical endpoint (early clinical response). Early clinical response was defined as substantial and sustained improvement that led the treating team to conclude the ECT course on clinical grounds, based on clinical judgment and supported by favorable CGI-S ratings. The dichotomization of patients into the ≤ 3 - and 4–5-session groups was based on both established clinical timelines and the empirical distribution of our data. The ≤ 3 -session threshold represents an acute safety-driven window. The earliest sessions of an ECT course are often

accompanied by acute neurobiological changes and may represent the period of greatest vulnerability to severe, treatment-limiting cognitive or medical adverse effects. Our findings support the clinical relevance of this cutoff, with the ≤ 3 -session group showing a sixteenfold increase in the adjusted odds of adverse-event-related termination (aOR=16.18, 95% CI: 9.70 to 26.97); 73.5% of patients in this subgroup discontinued treatment because of an adverse event or medical complication. The 4–5-session threshold captures a phase in which cumulative neuroplastic effects may begin to stabilize and transient influences, such as nonspecific effects of hospitalization or the initial effects of anesthesia, are less likely to contribute to the observed clinical response. Our findings support the clinical relevance of this group as a distinct treatment pattern, with 85.0% of courses ending because of early clinical response.

An important feature of the study design should be emphasized. Because the cohort was restricted to early-terminated courses, session number and reason for termination were not fully independent. Response-driven termination tended to occur after four or five sessions, whereas adverse-event-related termination often occurred earlier by necessity. Thus, part of the association between the shortest courses and adverse-event-related cessation is inherent in the cohort definition rather than representing a wholly independent empirical relationship. The adjusted and stratified analyses should be interpreted accordingly. They do not indicate that receiving fewer sessions causes adverse events. Rather, they demonstrate that the association between very short treatment exposure and adverse-event-related termination was consistent across diagnostic and ASA subgroups and was not explained by measured differences in case mix. The sixteenfold adjusted odds ratio therefore reflects the magnitude and consistency of this association, not an independent causal effect.

The adverse events leading to early termination were broadly consistent with the recognized medical morbidity of ECT. Neurological complications, principally postictal confusional states, were prominent, alongside respiratory and cardiovascular events. This pattern is consistent with the broader literature, in which postictal confusion and agitation are among the most frequently reported neuropsychiatric complications, while cardiovascular instability represents an important source of serious medical morbidity (13–17). The transient autonomic response to ECT, characterized by an initial parasympathetic surge followed by sympathetic activation, provides a plausible physiological basis

for peri-procedural cardiovascular events (1, 17). The concentration of treatment-limiting complications among patients receiving the fewest sessions suggests that, in susceptible patients, intolerance may become evident early in the treatment course.

A notable finding was that the association between session number and adverse-event-related termination persisted independently of psychiatric diagnosis and medical risk as measured by ASA physical status. In the adjusted models, no diagnostic group differed from the schizophrenia spectrum reference category, and ASA risk group was not a significant predictor of adverse-event-related termination. Stratified analyses similarly showed that the elevated termination rate in the ≤ 3 -session group was present across schizophrenia spectrum, bipolar, and depressive disorders and across both ASA categories. These findings are consistent with previous evidence suggesting that ECT-related adverse events may be more closely associated with physiological, seizure-related, and anesthetic factors than with psychiatric diagnosis or baseline illness severity (19–21). They also accord with evidence that somatic comorbidity, although relevant to general perioperative risk, does not consistently predict ECT outcomes (21). Susceptibility to treatment-limiting adverse events may therefore be difficult to anticipate from psychiatric presentation or a broad medical-risk classification alone, underscoring the importance of close monitoring during the initial sessions for all patients.

The clinical course after ECT cessation was among the most reassuring findings. Patients in the ≤ 3 -session group were substantially more severely ill at treatment termination, and this difference remained large after multiple imputation. However, the difference was no longer evident at hospital discharge. Patients in the ≤ 3 -session group also had a longer interval between their final ECT session and discharge, suggesting that additional inpatient management may have allowed further stabilization after the abbreviated course. However, the dataset did not capture the nature of post-cessation care, and the longer interval before discharge should not be interpreted as evidence of a specific stabilizing intervention. It may instead reflect recovery from the adverse event itself, adjustments to pharmacotherapy, or administrative factors influencing the timing of discharge. Although the existing literature provides no direct comparator for this finding, the results suggest that adverse-event-related early termination, while disrupting the expected treatment trajectory, does not necessarily preclude a satisfactory outcome when followed by

appropriate inpatient care. This observation should be considered hypothesis-generating and requires confirmation in prospective studies.

The groups also differed in sex distribution, with men overrepresented in the ≤ 3 -session group. This finding should be interpreted cautiously. Although some studies have reported a higher incidence of postictal agitation among men, this association has not consistently remained significant after multivariate adjustment, and large multisite studies suggest that ECT efficacy is not meaningfully influenced by sex (31, 32). The observed sex difference should therefore be interpreted as an incidental finding requiring replication rather than as evidence of a sex-specific susceptibility to early treatment termination.

Several limitations should be considered. First, the retrospective design is susceptible to information bias and precludes causal inference. Termination reasons were based on the treating team's contemporaneous clinical judgment rather than standardized adjudication. Second, the cohort was restricted to patients whose courses ended after five or fewer sessions and did not include a comparison group that completed a full acute course, limiting generalizability to the broader ECT population. Third, the adverse-event-related termination indicator is a patient-level binary measure that does not capture the number or timing of adverse events, nor events that did not lead to treatment termination. In addition, complication categories could not be stratified by a session group using the available data. Fourth, end-of-ECT and discharge CGI-S ratings were missing for a substantial proportion of patients, almost exclusively among early responders. Although this pattern was consistent with a missing-at-random assumption and was addressed using multiple imputation, residual bias cannot be excluded. The high proportion of missing CGI-S ratings likely reflects routine clinical practice rather than incomplete documentation, particularly the accelerated outpatient management and discharge of patients who achieved an early clinical response. Fifth, the study period (2019–2023) included the coronavirus disease 2019 (COVID-19) pandemic, during which ECT and anesthesia services were disrupted in many settings. Changes in case mix or ECT service availability during this period may have influenced treatment termination patterns, but calendar-year effects were not examined. Sixth, all treatments were administered using bifrontal electrode placement at a single center, which may limit generalizability to other electrode configurations and clinical settings. Finally, age and sex were excluded from adjusted models because of concern regarding collinearity. Alternative specifications that include these variables may yield different estimates.

CONCLUSION

Among early-terminated ECT courses, the number of sessions delivered is determined primarily by whether treatment ends because of an early clinical response or an adverse event. Adverse-event-related termination was concentrated among patients receiving the shortest ECT courses, independently of psychiatric diagnosis and medical risk, whereas the greater clinical severity observed at the time of ECT cessation was no longer evident by hospital discharge. These findings support close medical monitoring during the earliest ECT sessions and provide preliminary reassurance that adverse-event-related early termination, when followed by continued inpatient management, can be compatible with a favorable short-term clinical outcome. Prospective studies incorporating standardized adverse-event ascertainment and a comparison group completing a full ECT course are needed to confirm these findings and to clarify post-cessation recovery. Although our findings suggest that favorable short-term outcomes may be achievable after adverse-event-related early termination when followed by continued inpatient care, the mechanisms underlying this recovery remain unclear.

Ethical Approval: This study was approved by The Clinical Research Ethics Committee of the University of Health Sciences Bakirkoy Dr. Sadi Konuk Training and Research Hospital (2026-11-26 - 2026/197).

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RESEARCH ARTICLE

A comparison of metacognitive beliefs and social cognition in autogenous and reactive subtypes of adolescent obsessive-compulsive disorder

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ABSTRACT

Objective: Obsessive-compulsive disorder (OCD) is clinically heterogeneous, and the autogenous–reactive distinction may help characterize this heterogeneity. This study compared adolescents with reactive OCD, autogenous OCD, and healthy controls in terms of clinical characteristics, metacognitive beliefs, and social cognition, and examined associations between metacognitive beliefs and social cognition within OCD subtypes.

Method: This cross-sectional case-control study included 102 adolescents: 33 with reactive OCD, 31 with autogenous OCD, and 38 healthy controls. Diagnoses were confirmed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL). OCD severity, metacognitive beliefs, and social cognition were assessed using the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the Metacognitions Questionnaire for Children and Adolescents, the Reading the Mind in the Eyes Test, and the Faux Pas Test. Group comparisons and correlation analyses were performed.

Results: The reactive and autogenous OCD groups differed primarily in symptom content, with cleaning and checking symptoms more common in the reactive group and religious and sexual obsessions more common in the autogenous group. The OCD subtypes did not differ in overall OCD severity or global functioning. After correction for multiple comparisons, metacognitive belief domains differed across groups; however, post hoc analyses revealed no significant differences between the two OCD subtypes. No significant group differences were observed in social cognition measures. Correlation analyses suggested selective associations between metacognitive beliefs and social understanding, particularly in the autogenous group.

Conclusion: In adolescent OCD, the autogenous–reactive distinction appears to reflect differences in symptom content rather than distinct metacognitive or social cognitive profiles. Larger longitudinal studies are needed to clarify subtype-related cognitive heterogeneity.

Keywords: Obsessive-compulsive disorder, adolescent, metacognition, social cognition, theory of mind

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a heterogeneous disorder with respect to symptom

content and clinical presentation (1). One of the most widely used approaches to characterizing this heterogeneity is the classification of obsessions into autogenous and reactive subtypes (2). According to

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the model proposed by Lee and Kwon, autogenous obsessions consist of ego-dystonic thoughts that typically arise without an identifiable external trigger and often involve aggressive, sexual, or moral/religious themes. In contrast, reactive obsessions are centered on fears elicited by external stimuli, such as contamination, making mistakes, causing harm, or disruptions of symmetry, and are frequently accompanied by observable compulsions such as washing, checking, or ordering (2). Previous studies have shown that these two obsession types differ not only in content but also in their triggering patterns, subjective experiences, and coping strategies (3, 4).

Metacognition refers to higher-order cognitive processes through which individuals monitor, evaluate, and regulate their own thinking (5, 6). In OCD, it is widely accepted that not only the content of obsessive thoughts but also the interpretation of these thoughts as dangerous, meaningful, or requiring control plays a central role in maintaining the disorder. Dysfunctional metacognitive beliefs are more pronounced in individuals with OCD than in healthy controls and are associated with symptom severity (7, 8). Studies in pediatric populations have similarly demonstrated associations between maladaptive metacognitive beliefs and OCD (5, 9, 10). However, it remains unclear whether these associations differ between the autogenous and reactive subtypes in children and adolescents.

Social cognition encompasses the cognitive processes that enable individuals to understand their own and others' emotions, intentions, and mental states within social contexts. In OCD, impairments have been reported particularly in theory of mind, cognitive empathy, and certain aspects of emotion recognition (11, 12). Although metacognition and social cognition are conceptually related, they represent distinct constructs: metacognition concerns the monitoring and evaluation of one's own mental processes, whereas social cognition involves understanding the mental states of others and navigating interpersonal interactions (13). Associations between these domains have been documented across psychiatric disorders (13). However, studies directly examining the relationship between metacognition and social cognition in individuals with OCD remain limited. Existing evidence suggests that dysfunctional metacognitive beliefs in OCD may contribute to psychosocial impairment and may partially overlap with social cognitive processes, although the nature of this relationship remains unclear (14, 15).

Consequently, metacognition and social cognition may be viewed as distinct yet potentially interacting higher-order cognitive domains. In OCD, maladaptive beliefs about intrusive thoughts, responsibility, threat, and cognitive control may influence not only how individuals interpret their own mental experiences but also how they perceive and interpret socially relevant situations. Nevertheless, studies investigating metacognitive beliefs and social cognition simultaneously within the autogenous and reactive OCD subtypes are scarce, particularly in adolescent populations. Examining these relationships during adolescence may provide further insight into the cognitive mechanisms underlying OCD.

Accordingly, examining autogenous and reactive obsession patterns alongside metacognitive beliefs and social cognition may improve our understanding of the cognitive heterogeneity of adolescent OCD. However, studies integrating these domains within a single framework remain limited, especially in adolescent samples. In the present study, adolescents with autogenous OCD, reactive OCD, and healthy controls were compared with respect to metacognitive beliefs and social cognition. In addition, correlations between metacognitive belief domains and measures of social cognition were examined separately within the autogenous and reactive OCD groups to determine whether these constructs were independent or selectively associated within each subtype. Based on previous findings suggesting that autogenous obsessions are more internally generated, ego-dystonic, and more closely linked to the appraisal of intrusive thoughts, we hypothesized that subtype-related differences would be more evident in metacognitive beliefs. Analyses of social cognition and its associations with metacognitive beliefs were conducted to explore whether subtype-related heterogeneity also extends to the interpretation of emotions, intentions, and socially relevant interpersonal situations. Through this integrated approach, the study aimed to clarify the relationships among OCD subtypes, metacognitive beliefs, and social cognition in adolescents with OCD.

METHODS

Study Design and Sample

This cross-sectional, comparative case-control study was designed to compare the autogenous and reactive subtypes of adolescent OCD in terms of metacognitive beliefs and social cognition. The study

was conducted at the Child and Adolescent Psychiatry Outpatient Clinic of Basaksehir Cam and Sakura City Hospital, Istanbul, Türkiye. The sample comprised 102 adolescents: 33 with reactive OCD, 31 with autogenous OCD, and 38 healthy controls.

All participants, including adolescents with OCD and healthy controls, were evaluated using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) (16). The OCD group included adolescents who were evaluated by a child and adolescent psychiatrist and whose diagnosis of OCD was confirmed using the K-SADS-PL. The healthy control group consisted of volunteers with sociodemographic characteristics comparable to those of the OCD group. Healthy controls were also screened using the K-SADS-PL, and those who met the criteria for any psychiatric disorder were excluded.

Adolescents with sufficient cognitive capacity to complete the assessment instruments were eligible for inclusion. Participants with a psychotic disorder, bipolar disorder, neurological disease, or any other clinical condition that could interfere with the assessment process were excluded.

The distinction between the autogenous and reactive OCD subtypes was based on the predominant obsession pattern, in accordance with Lee and Kwon's classification model, which considers the mode of emergence and content of obsessions. Subtype assignment was made by the evaluating clinicians during the clinical assessment. Participants with predominantly aggressive, sexual, religious, magical, or somatic obsessions were classified as having autogenous OCD, whereas those with predominantly cleaning, checking, repetitive, counting, or symmetry/ordering symptoms were classified as having reactive OCD.

In participants with multiple symptom dimensions, subtype classification was based on the obsessive-compulsive symptom pattern that was most prominent in the clinical presentation, caused the greatest subjective distress, and had the greatest effect on daily functioning. Accordingly, adolescents with both autogenous and reactive symptom features were assigned to the subtype that best represented their predominant clinical presentation. A mixed symptom profile, defined as the presence of at least one autogenous and one reactive symptom dimension, was observed in 40 participants with OCD (62.5%). In these cases, subtype assignment was made based on the predominant symptom pattern identified during the clinical assessment.

Data Collection Instruments

A sociodemographic and clinical data form developed by the researchers was completed for all participants. The form recorded age, sex, educational level, clinical diagnosis, illness duration, psychiatric comorbidities, medication use, and other relevant clinical characteristics.

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

OCD symptom severity was assessed using the Children's Yale-Brown Obsessive Compulsive Scale. The CY-BOCS is a clinician-administered, semistructured interview used to assess the type and severity of obsessive-compulsive symptoms in children and adolescents (17). The assessment is based on information obtained from both the child and the parent, together with the clinician's judgment. Current obsessions and compulsions are first identified, after which symptom severity is rated according to the time occupied by symptoms, functional interference, symptom-related distress, resistance, and degree of control. The scale yields separate obsession and compulsion severity scores and a total severity score calculated as the sum of the two subscale scores. Total scores range from 0 to 40, with higher scores indicating greater OCD severity. The interrater reliability and clinical utility of the Turkish version have been demonstrated by Yücelen et al. (18).

Metacognitions Questionnaire for Children and Adolescents

Metacognitive beliefs were assessed using the Metacognitions Questionnaire for Children and Adolescents. The questionnaire was developed by Bacow et al. to assess metacognitive beliefs and appraisals related to thought processes in children and adolescents (19). It was adapted from the adolescent measure developed by Cartwright-Hatton et al. and modified for use in child and adolescent populations. The questionnaire consists of 24 items across four subdomains: cognitive monitoring, positive meta-worry, negative meta-worry, and superstitious, punishment, and responsibility beliefs. Each item is rated on a 4-point Likert scale ranging from 1 ("strongly disagree") to 4 ("strongly agree"). Total scores range from 24 to 96, with higher scores indicating greater maladaptive metacognitive activity. The total score was used to assess metacognitive beliefs. The Turkish standardization, validity, and reliability study was conducted by Irak (20).

Reading the Mind in the Eyes Test (RMET)

Social cognition was assessed using the Reading the Mind in the Eyes Test (RMET). The RMET is a performance-based measure of social cognition that evaluates the ability to infer another person's mental or emotional state from photographs showing only the eye region of the face. It assesses theory of mind and emotion recognition abilities. For each item, participants select the mental-state descriptor that best corresponds to the eye-region image presented. Correct responses are awarded one point, and higher total scores indicate better theory of mind and social cognition performance (21). The RMET total score was used in the analyses. The Turkish reliability study was conducted by Yıldırım et al. (22) and the psychometric properties of the Turkish child and adult forms were examined by Girli (23).

Faux Pas Test

An additional dimension of social cognition was assessed using the Faux Pas Test. This performance-based measure evaluates the ability to detect socially inappropriate, hurtful, or tactless remarks and to understand the underlying intentions, emotions, and false beliefs. Participants listen to or read brief social stories and then answer questions about whether a faux pas occurred, who made it, why it was inappropriate, and what the characters thought or felt (24). The detection, identification, understanding, and false-belief subdomains, as well as the total Faux Pas score, were evaluated. Higher scores indicate better social cognition and theory of mind performance. The Turkish adaptation and psychometric properties of the child version of the Faux Pas Recognition Test were examined by Şahin et al. in a sample of children and adolescents aged 9–17 years (25).

Children's Global Assessment Scale (CGAS)

Overall functioning was assessed using the Children's Global Assessment Scale. The CGAS is a clinician-rated, unidimensional scale developed to evaluate overall functioning in children and adolescents. It provides a global assessment of psychological, social, and academic functioning. Scores range from 1 to 100, with higher scores indicating better overall functioning and lower scores indicating greater functional impairment (26). The CGAS score was used to assess participants' overall functioning.

Procedure

Clinical and sociodemographic data were obtained through clinical interviews and medical records. All

assessment instruments were administered under standardized conditions. In the OCD group, obsession content was reviewed in detail, and each participant was assigned to the autogenous or reactive subtype according to the predominant symptom pattern. Healthy controls were screened to confirm the absence of any current or lifetime psychiatric disorder.

Ethical Approval

The study was approved by the Clinical Research Ethics Committee of Basaksehir Cam and Sakura City Hospital on April 8, 2025 (approval no. KAEK-11/26.03.2025.116). The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent and assent were obtained from all participants and their parents.

Statistical Analysis

Statistical analyses were performed using jamovi version 2.6 (27), with a two-tailed significance level of $p < 0.05$. The distributions of continuous variables were assessed using the Shapiro–Wilk test. Continuous variables are presented as the mean $\pm$ standard deviation or median [25th–75th percentile], according to their distribution, whereas categorical variables are summarized as frequencies and percentages.

Sociodemographic characteristics and parental psychiatric history were compared among the reactive OCD, autogenous OCD, and healthy control groups. Welch's analysis of variance (ANOVA) was used for normally distributed continuous variables when parametric assumptions were met, whereas the Kruskal–Wallis test was used for nonnormally distributed variables. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. These baseline comparisons were used to characterize the study groups and were interpreted descriptively.

Clinical characteristics and treatment-related variables were evaluated only among participants with OCD because these variables were not applicable to healthy controls. The reactive and autogenous OCD groups were compared in terms of the duration of psychiatric symptoms, time from symptom onset to diagnosis, duration of medication use, psychotropic medication use, and history of cognitive behavioral therapy. Continuous clinical variables were analyzed using the Mann–Whitney U test because they did not meet the assumption of normality. Categorical treatment-related variables were analyzed using the chi-square test or Fisher's exact test, as appropriate.

Table 1: Comparison of clinical, metacognitive, and social cognition measures among adolescents with reactive obsessive-compulsive disorder (OCD), autogenous OCD, and healthy controls

Variables	Reactive OCD (n=33)	Autogenous OCD (n=31)	HC (n=38)	p	FDR- adjusted p	Effect size
CGAS	55.0 [50.0–62.0]	52.0 [49.0–60.0]	75.5 [72.0–80.8]	<0.001^a	0.007^a	$\epsilon^2=0.695$
Total CY-BOCS	21.3±6.24	19.4±7.02	–	0.33	0.429	d=0.29
Metacognitions Questionnaire for Children and Adolescents						
Metacognitive beliefs (total score)	62.0 [57.0–70.0]	67.0 [59.5–75.0]	61.0 [57.0–64.0]	0.008^b	0.029^b	$\epsilon^2=0.095$
Positive meta-worry	11.0 [8.0–12.0]	12.0 [8.0–16.0]	11.0 [10.0–13.0]	0.411	0.445	$\epsilon^2=0.018$
Negative meta-worry	18.0 [16.0–21.0]	20.0 [17.0–22.5]	15.0 [12.0–18.0]	<0.001^c	0.007^c	$\epsilon^2=0.141$
Superstitious/responsibility-punishment beliefs	17.0 [12.0–21.0]	18.0 [16.0–21.0]	15.0 [11.3–17.8]	0.009^b	0.029^b	$\epsilon^2=0.092$
Cognitive monitoring	18.0 [15.0–21.0]	18.0 [16.0–21.0]	17.0 [15.0–18.8]	0.076	0.197	$\epsilon^2=0.051$
Theory of Mind (ToM)						
RMET	20.0 [19.0–21.0]	20.0 [18.0–22.0]	21.0 [19.0–22.0]	0.372	0.440	$\epsilon^2=0.020$
Faux Pas total	37.0 [33.0–38.0]	36.0 [33.0–38.0]	37.0 [36.0–39.0]	0.106	0.197	$\epsilon^2=0.045$
Faux Pas Detection	10.0 [9.0–10.0]	9.0 [8.5–10.0]	10.0 [9.0–10.0]	0.152	0.230	$\epsilon^2=0.038$
Faux Pas Identification	10.0 [9.0–10.0]	9.0 [7.5–10.0]	10.0 [9.0–10.0]	0.102	0.197	$\epsilon^2=0.046$
Faux Pas Understanding	10.0 [10.0–10.0]	10.0 [10.0–10.0]	10.0 [10.0–10.0]	0.973	0.973	$\epsilon^2=0.001$
False-belief attribution	8.0 [6.0–9.0]	8.0 [7.0–9.0]	9.0 [7.8–10.0]	0.159	0.230	$\epsilon^2=0.037$

Values are presented as median [25th–75th percentile], except for Total CY-BOCS, which is presented as mean ± standard deviation. OCD: Obsessive-compulsive disorder; HC: Healthy controls; CGAS: Children's Global Assessment Scale; CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale; RMET: Reading the Mind in the Eyes Test; ToM: Theory of mind. Three-group comparisons were performed using the Kruskal–Wallis test. Total CY-BOCS scores were compared only between the reactive and autogenous OCD groups. False discovery rate (FDR)-adjusted p values were calculated using the Benjamini–Hochberg procedure for all comparisons reported in this table. Effect sizes are reported as epsilon-squared (ϵ^2) for Kruskal–Wallis tests and Cohen's d for the CY-BOCS comparison. Post hoc comparisons were performed using the Dwass–Steel–Critchlow–Fligner test. Superscript letters indicate significant pairwise group differences. ^aHC > Reactive OCD ≈ Autogenous OCD; ^bAutogenous OCD > HC; Reactive OCD ≈ Autogenous OCD and Reactive OCD ≈ HC; ^cReactive OCD ≈ Autogenous OCD > HC.

Global functioning, metacognitive beliefs, and social cognition measures were compared among the reactive OCD, autogenous OCD, and healthy control groups using the Kruskal–Wallis test. When an omnibus test was significant, post hoc pairwise comparisons were performed using the Dwass–Steel–Critchlow–Fligner test. The total CY-BOCS score was compared only between the reactive OCD and autogenous OCD groups because this measure was not applicable to healthy controls.

To control the risk of Type I error due to multiple testing, the Benjamini–Hochberg false discovery rate (FDR) procedure was applied to the comparisons reported in Table 1. Both unadjusted and FDR-adjusted p values are reported.

Associations between metacognitive beliefs and social cognition measures were examined separately in the reactive and autogenous OCD groups using Spearman's rank correlation analysis. Separate correlation matrices were constructed for each OCD subgroup.

Effect sizes were reported as eta-squared (η^2) for Welch's ANOVA, epsilon-squared (ϵ^2) for Kruskal–

Wallis tests, Cramér's V for three-group categorical comparisons, rank-biserial correlation (r_{rb}) for Mann–Whitney U tests, Cohen's d for two-group parametric comparisons, and phi (ϕ) for two-group categorical comparisons.

A formal a priori power analysis was not conducted because the sample was determined by the number of eligible participants available during the study period. A sensitivity power analysis was therefore performed using G*Power to estimate the minimum detectable effect size for the available sample. For three-group comparisons with a total sample size of 102, $\alpha=0.05$, and 80% power, the minimum detectable effect size was $f=0.31$, corresponding to $\eta^2 \approx 0.089$. For pairwise comparisons between the reactive and autogenous OCD groups, with sample sizes of $n=33$ and $n=31$, respectively, the minimum detectable effect size was approximately Cohen's $d=0.71$. These estimates indicate that the study was adequately powered to detect medium-to-large effects, whereas smaller effects may have remained undetected.

Table 2: Sociodemographic, parental psychiatric history, and clinical treatment characteristics of the study groups

Variables	Reactive OCD (n=33)	Autogenous OCD (n=31)	HC (n=38)	p	Effect size
Age, years	15.4±2.28	15.2±1.90	15.0±2.55	0.812	$\eta^2=0.005$
Male sex, n (%)	18 (54.5)	15 (48.4)	19 (50.0)	0.880	$V=0.051$
School grade	9.64±2.06	9.39±1.94	8.92±2.44	0.411	$\eta^2=0.020$
Grade repetition, n (%)	5 (15.2)	4 (12.9)	0 (0.0)	0.051	$V=0.242$
Maternal psychiatric diagnosis, n (%)	7 (21.2)	7 (22.6)	2 (5.3)	0.082	$V=0.226$
Maternal psychiatric treatment, n (%)	6 (18.2)	6 (19.4)	2 (5.3)	0.159	$V=0.194$
Paternal psychiatric diagnosis, n (%)	7 (21.2)	7 (22.6)	0 (0.0)	0.008	$V=0.308$
Paternal psychiatric treatment, n (%)	7 (21.2)	4 (12.9)	0 (0.0)	0.014	$V=0.288$
Clinical characteristics and treatment variables					
Duration of psychiatric complaints, months	41.42±17.53	34.26±21.16	—	0.165	$r_{r\beta}=0.203$
Time from symptom onset to diagnosis, months	21.13±18.85	19.30±17.92	—	0.707	$r_{r\beta}=0.057$
Duration of medication use, months	13.25±14.19	9.17±14.67	—	0.146	$r_{r\beta}=0.215$
Antipsychotic use, n (%)	15/32 (46.9)	8/30 (26.7)	—	0.103	$\phi=0.209$
SSRI use, n (%)	28/32 (87.5)	22/30 (73.3)	—	0.163	$\phi=0.179$
Other antidepressant use, n (%)	2/32 (6.3)	1/30 (3.3)	—	0.600	$\phi=0.068$
Mood stabilizer use, n (%)	3/32 (9.4)	1/30 (3.3)	—	0.341	$\phi=0.123$
Benzodiazepine use, n (%)	3/32 (9.4)	0/30 (0.0)	—	0.088	$\phi=0.218$
Stimulant medication use, n (%)	2/32 (6.3)	1/30 (3.3)	—	0.593	$\phi=0.068$
CBT, n (%)	11/33 (33.3)	7/30 (23.3)	—	0.388	$\phi=0.111$

Values are presented as mean ± standard deviation or n (%). OCD: Obsessive-compulsive disorder; HC: Healthy controls; SSRI: Selective serotonin reuptake inhibitor; CBT: Cognitive behavioral therapy. Sociodemographic variables were compared among the reactive OCD, autogenous OCD, and healthy control groups. Clinical characteristics and treatment-related variables were compared only between the reactive OCD and autogenous OCD groups, as these variables were not applicable to healthy controls. Continuous sociodemographic variables were analyzed using Welch's ANOVA, whereas categorical sociodemographic variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous clinical variables were analyzed using the Mann-Whitney U test, and categorical treatment-related variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Effect sizes are reported as eta-squared (η^2) for Welch's ANOVA, Cramér's V for three-group categorical comparisons, rank-biserial correlation ($r_{r\beta}$) for Mann-Whitney U tests, and phi (ϕ) for two-group categorical comparisons.

RESULTS

A total of 102 adolescents were included in the study: 33 with reactive OCD, 31 with autogenous OCD, and 38 healthy controls. The groups were comparable in age, sex distribution, and school grade. Grade repetition showed a borderline group difference among the groups but did not reach statistical significance. Maternal psychiatric diagnosis and treatment history did not differ significantly among the groups. Paternal psychiatric diagnosis and treatment history differed among the groups and were more common in the OCD groups than in healthy controls. These baseline comparisons were interpreted descriptively. The sociodemographic characteristics and parental psychiatric histories of the study groups are presented in Table 2.

Clinical and treatment-related variables were evaluated only among participants with OCD. The reactive and autogenous OCD groups did not differ significantly in the duration of psychiatric symptoms,

time from symptom onset to diagnosis, duration of medication use, antipsychotic use, selective serotonin reuptake inhibitor (SSRI) use, use of other antidepressants, mood stabilizer use, benzodiazepine use, stimulant use, or history of cognitive behavioral therapy. The clinical and treatment-related characteristics of the OCD subgroups are presented in Table 2.

Psychiatric comorbidities were also compared between the reactive and autogenous OCD groups. The most common comorbidities in the OCD sample were specific phobia, generalized anxiety disorder, major depressive disorder, and attention-deficit/hyperactivity disorder (ADHD). Specific phobia was more common in the reactive OCD group, whereas generalized anxiety disorder was numerically more common in the autogenous OCD group, although this difference did not reach statistical significance. ADHD and other psychiatric comorbidities did not differ significantly between the two OCD subgroups. These findings are presented in Table 3.

Table 3: Psychiatric comorbidities in adolescents with reactive and autogenous obsessive-compulsive disorder (OCD)

Psychiatric comorbidity	Reactive OCD (n=33) n (%)	Autogenous OCD (n=31) n (%)	p	Effect size
Specific phobia	16 (48.5)	7 (22.6)	0.039	$\phi=0.270$
Generalized anxiety disorder	8 (24.2)	14 (45.2)	0.114	$\phi=0.220$
Major depressive disorder	12 (36.4)	7 (22.6)	0.280	$\phi=0.151$
ADHD	10 (30.3)	8 (25.8)	0.784	$\phi=0.050$
Social anxiety disorder	8 (24.2)	5 (16.1)	0.539	$\phi=0.101$
Tic disorder	7 (21.2)	6 (19.4)	1.000	$\phi=0.023$
Separation anxiety disorder	4 (12.1)	7 (22.6)	0.331	$\phi=0.139$
Dissociative symptoms/disorder	8 (24.2)	2 (6.5)	0.083	$\phi=0.245$
History of nonsuicidal self-injury (NSSI)	3 (9.1)	5 (16.1)	0.468	$\phi=0.106$
Suicidality	5 (15.2)	2 (6.5)	0.428	$\phi=0.139$
Eating disorder	4 (12.1)	2 (6.5)	0.673	$\phi=0.097$
Oppositional defiant disorder	4 (12.1)	1 (3.2)	0.356	$\phi=0.166$
Panic disorder	2 (6.1)	2 (6.5)	1.000	$\phi=0.008$
Specific learning disorder	1 (3.0)	1 (3.2)	1.000	$\phi=0.006$
History of hypomania/mania	0 (0.0)	1 (3.2)	0.484	$\phi=0.130$

The distribution of obsession and compulsion symptom dimensions differed between the OCD subtypes. In the reactive OCD group, cleaning was the most frequently endorsed symptom dimension, followed by checking and counting. In the autogenous OCD group, religious symptoms were the most common, followed by checking, cleaning, and sexual symptoms. Aggressive and sexual symptoms were more prominent in the autogenous group, whereas cleaning symptoms were more characteristic of the reactive group. Hoarding and somatic symptoms were relatively uncommon in both OCD subgroups. The distribution of obsession and compulsion symptom dimensions in the reactive and autogenous OCD groups is shown in Figure 1.

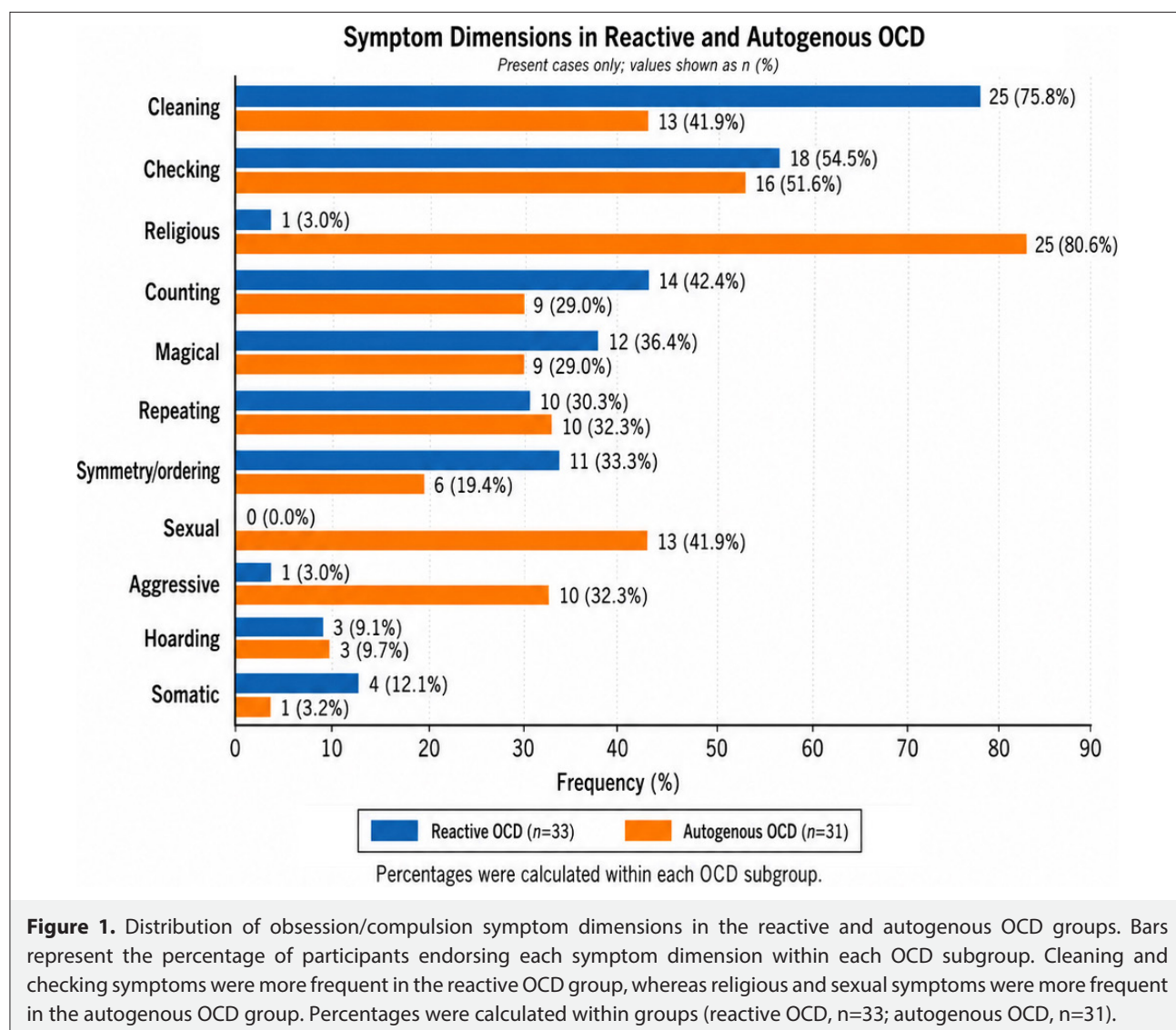
Comparisons of clinical, metacognitive, and social cognition measures among the reactive OCD, autogenous OCD, and healthy control groups are summarized in Table 1. After Benjamini–Hochberg FDR correction, the overall pattern of findings remained unchanged. Significant group differences remained for CGAS scores, total metacognitive beliefs, negative meta-worry beliefs, and superstitious and responsibility/punishment beliefs. No social cognition measure differed significantly among the groups after FDR correction.

CGAS scores differed significantly among the groups, $\chi^2(2)=70.15$, $p<0.001$, FDR-adjusted $p=0.007$, $\varepsilon^2=0.695$. Post hoc comparisons indicated that healthy controls had significantly higher CGAS scores

than both OCD groups, whereas the reactive and autogenous OCD groups did not differ significantly from each other.

Total metacognitive belief scores also differed significantly among the groups, $\chi^2(2)=9.56$, $p=0.008$, FDR-adjusted $p=0.029$, $\varepsilon^2=0.095$. Post hoc comparisons showed that the autogenous OCD group had higher total metacognitive belief scores than healthy controls, whereas the reactive OCD group did not differ significantly from either the autogenous OCD group or healthy controls. Negative meta-worry beliefs differed significantly among the groups, $\chi^2(2)=14.27$, $p<0.001$, FDR-adjusted $p=0.007$, $\varepsilon^2=0.141$. Both OCD groups had higher negative meta-worry belief scores than healthy controls, with no significant difference between the reactive and autogenous OCD groups. Superstitious and responsibility/punishment beliefs also differed significantly among the groups, $\chi^2(2)=9.32$, $p=0.009$, FDR-adjusted $p=0.029$, $\varepsilon^2=0.092$. Post hoc comparisons indicated that the autogenous OCD group scored higher than healthy controls, whereas the reactive OCD group did not differ significantly from either group.

No significant group differences were found in positive meta-worry beliefs, cognitive monitoring, RMET scores, Faux Pas Detection, Faux Pas Identification, Faux Pas Understanding, False Belief Attribution, or total Faux Pas scores. Total CY-BOCS scores did not differ significantly between the reactive and autogenous OCD groups.



In the reactive OCD group, total metacognitive belief scores were not significantly associated with RMET or Faux Pas measures. Significant correlations were observed primarily among the metacognitive subdomains and among the Faux Pas subcomponents. Negative meta-worry beliefs were positively correlated with superstitious and responsibility/punishment beliefs and with cognitive monitoring. Total metacognitive belief scores were positively correlated with negative meta-worry beliefs, superstitious and responsibility/punishment beliefs, and cognitive monitoring. Among the Faux Pas subcomponents, total Faux Pas scores were positively correlated with Faux Pas Detection, Faux Pas Identification, and False Belief Attribution. Faux Pas Detection and Faux Pas Identification scores were identical across participants in the reactive OCD group, resulting in a correlation coefficient of $r=1.000$

between these two subdomains. The data and scoring for these variables were rechecked, and the coefficient was retained because it reflected complete overlap between the two subdomain scores in this subgroup. The correlation matrix for the reactive OCD group is presented in Table 4.

In the autogenous OCD group, total metacognitive belief scores were positively correlated with Faux Pas Understanding. Negative meta-worry beliefs and superstitious and responsibility/punishment beliefs were also positively associated with Faux Pas Understanding. Significant correlations were additionally observed among the metacognitive subdomains and among the Faux Pas subcomponents. Total Faux Pas scores were positively correlated with Faux Pas Detection, Faux Pas Identification, and False Belief Attribution. Overall, associations between metacognitive domains and social cognition

Table 4: Correlation matrix for the reactive obsessive-compulsive disorder (OCD) group

No.	Variables	1	2	3	4	5	6	7	8	9	10	11
1	Positive meta-worry	—										
2	Negative meta-worry	-0.110	—									
3	Superstitious/responsibility-punishment beliefs	-0.068	0.589***	—								
4	Cognitive monitoring	0.142	0.582***	0.386*	—							
5	Metacognitive beliefs (total)	0.227	0.765***	0.777***	0.773***	—						
6	RMET	0.223	-0.224	-0.107	-0.194	-0.058	—					
7	Faux pas detection	-0.061	0.124	0.084	-0.031	0.060	0.124	—				
8	Faux pas identification	-0.061	0.124	0.084	-0.031	0.060	0.124	1.000***	—			
9	Faux pas understanding	-0.045	-0.114	0.058	0.084	0.029	0.186	0.228	0.228	—		
10	False-belief attribution	0.279	-0.088	-0.028	-0.139	-0.012	0.142	-0.082	-0.082	-0.034	—	
11	Faux pas total	0.144	0.069	0.039	0.047	0.106	0.211	0.655***	0.655***	0.236	0.598***	—

Values are presented as Spearman's rank correlation coefficients. OCD: Obsessive-compulsive disorder; RMET: Reading the Mind in the Eyes Test. Faux Pas Detection and Faux Pas Identification scores were identical in the reactive OCD group, resulting in a correlation coefficient of $r=1.000$. The data and scoring were verified, and no data entry or scoring errors were identified. This value was therefore retained because it reflected complete overlap between the two subdomain scores in this subgroup. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table 5: Correlation matrix for the autogenous obsessive-compulsive disorder (OCD) group

No.	Variables	1	2	3	4	5	6	7	8	9	10	11
1	Positive meta-worry	—										
2	Negative meta-worry	-0.102	—									
3	Superstitious/responsibility-punishment beliefs	-0.095	0.772***	—								
4	Cognitive monitoring	0.070	0.336	0.299	—							
5	Metacognitive beliefs (total)	0.360*	0.746***	0.755***	0.646***	—						
6	RMET	-0.079	0.261	0.302	0.303	0.306	—					
7	Faux Pas Detection	0.200	0.019	0.021	0.009	0.114	0.017	—				
8	Faux Pas Identification	0.105	-0.011	-0.023	-0.050	0.034	0.105	0.877***	—			
9	Faux Pas Understanding	0.140	0.367*	0.407*	0.224	0.464**	0.232	0.203	0.327	—		
10	False-belief attribution	0.025	-0.254	0.053	-0.058	-0.107	0.076	-0.022	0.056	-0.049	—	
11	Faux Pas total	0.160	-0.144	0.077	-0.039	0.025	0.099	0.691***	0.747***	0.279	0.621***	—

Values are presented as Spearman's rank correlation coefficients. OCD: Obsessive-compulsive disorder; RMET: Reading the Mind in the Eyes Test. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

measures were limited and were most evident for Faux Pas Understanding in the autogenous OCD group. The correlation matrix for the autogenous OCD group is presented in Table 5.

DISCUSSION

This study examined metacognitive beliefs and social cognition in adolescents with reactive and autogenous OCD compared with healthy controls. Overall, the findings suggest that the autogenous–reactive distinction was reflected primarily in symptom content and metacognitive beliefs, whereas group-level differences in social cognition were less apparent.

Before interpreting the subtype-related findings, the clinical characteristics of the study groups should be considered. The groups were broadly comparable in age, sex distribution, and school grade, suggesting that the principal findings were unlikely to be attributable to major sociodemographic differences. The higher frequency of paternal psychiatric diagnoses and treatment histories in the OCD groups may reflect broader familial vulnerability to OCD and related psychopathology. This interpretation is consistent with previous studies emphasizing the contribution of familial and developmental factors to early-onset pediatric OCD (28, 29). However, this pattern was observed in both OCD subgroups and should therefore not be interpreted as specific to either the reactive or autogenous subtype.

Treatment-related variables were also generally similar between the two OCD subgroups. The absence of significant differences in medication use or history of cognitive behavioral therapy suggests that the observed subtype-related findings were unlikely to be explained primarily by treatment exposure. Psychiatric comorbidities likewise did not show a clear subtype-specific pattern. Anxiety disorders and major depressive disorder were observed in both OCD subgroups, consistent with previous pediatric OCD literature indicating that anxiety and depressive disorders commonly co-occur with OCD in children and adolescents (30, 31). However, the overall comorbidity profile did not indicate a clear separation between the reactive and autogenous subtypes. Taken together, these background findings suggest that the two OCD groups were clinically comparable in many respects while also displaying the familial burden and comorbidity patterns commonly observed in pediatric OCD.

The reactive and autogenous OCD groups did not differ significantly in total metacognitive belief scores or in most metacognitive subdomains. This finding suggests that maladaptive metacognitive beliefs may represent a broader cognitive feature of OCD rather than a clearly subtype-specific marker. Nevertheless, comparisons with healthy controls indicated that metacognitive beliefs were not entirely independent of subtype-related symptom patterns. The autogenous OCD group had higher total metacognitive belief scores and higher superstitious and responsibility/punishment belief scores than healthy controls, whereas both OCD groups had higher negative meta-worry belief scores than healthy controls.

Adult studies of the autogenous–reactive distinction have yielded inconsistent findings. Some studies have reported higher scores on the 30-item Metacognitions Questionnaire (MCQ-30), including both total and subscale scores, in individuals with autogenous obsessions than in those with reactive obsessions, suggesting that secondary beliefs about thoughts may be more pronounced in autogenous presentations (32). In contrast, other studies have found comparable levels of metacognitive pathology across OCD subtypes (33). Thus, the adult literature does not provide a definitive conclusion as to whether metacognitive beliefs constitute a consistent and specific marker of the autogenous–reactive distinction. Direct evidence comparing autogenous and reactive OCD in pediatric samples remains limited. Recent pediatric OCD research has identified distinct metacognitive profiles, with more maladaptive metacognitive beliefs associated with older age, greater OCD severity, aggressive, sexual, and religious obsessions, and internalizing symptoms (10). Similarly, studies of children and adolescents with OCD have suggested that metacognitive beliefs may be more closely related to particular symptom dimensions, especially obsessing and doubting/checking symptoms (34). These findings indirectly support an association between metacognitive beliefs and symptom content resembling the autogenous cluster, but they do not establish metacognition as a categorical subtype marker. Taken together, the present findings suggest that metacognitive heterogeneity in adolescent OCD cannot be reduced to the autogenous–reactive dichotomy. Rather, metacognitive beliefs may represent a shared cognitive vulnerability that varies according to symptom content, clinical severity, developmental characteristics, and broader internalizing psychopathology.

With respect to social cognition, no significant group differences were found in RMET or Faux Pas performance after correction for multiple comparisons. This finding suggests that social cognition may not represent a broad or homogeneous distinguishing feature of the autogenous and reactive OCD subtypes in adolescence. It is consistent with previous literature showing that social cognitive difficulties are not uniformly observed across OCD samples or assessment tasks (11, 12). Reviews and meta-analyses of adult OCD have reported impairments particularly in theory of mind and cognitive empathy, while also emphasizing that the magnitude of these impairments varies according to the task and social cognitive domain assessed (11). Similarly, task-based studies have suggested that basic social cognitive abilities may remain relatively preserved in OCD, whereas more complex mentalizing processes may be more vulnerable (35).

Although group-level differences in social cognition were not evident, the correlation findings suggested a more selective relationship between metacognitive beliefs and specific aspects of social understanding. In the reactive group, significant associations were largely confined within the same domain, suggesting relative separation between metacognitive beliefs and social cognition. In contrast, in the autogenous group, more maladaptive metacognitive beliefs were associated with better performance in interpreting the meaning, intention, and interpersonal consequences of socially inappropriate situations. Rather than indicating global social cognitive impairment, this pattern may reflect a selective association between beliefs about intrusive thoughts and the processing of complex social meaning in adolescents with autogenous OCD. An exploratory pilot study examining social cognition and metacognition concurrently similarly suggested that basic social cognitive abilities may be relatively preserved in OCD, whereas metacognitive disturbances may be more prominent (15). Taken together, the present findings suggest that metacognition and social cognition in adolescent OCD are neither entirely independent nor components of a single unified dimension of impairment. Instead, their relationship may emerge through selective associations between specific metacognitive belief domains and particular aspects of social understanding.

Several limitations should be considered when interpreting these findings. First, the cross-sectional design precludes causal inferences regarding the relationships among OCD subtype, metacognitive

beliefs, and social cognition. Second, the study was conducted at a single tertiary child and adolescent psychiatry outpatient clinic, and the autogenous and reactive OCD subgroups were relatively small. Although the sensitivity power analysis indicated that the available sample was sufficient to detect medium-to-large effects, smaller effects, particularly in pairwise comparisons between the OCD groups, may have remained undetected. The generalizability of the findings may therefore be limited, and nonsignificant results should be interpreted cautiously. Third, although subtype classification was based on Lee and Kwon's theoretical model, assignment to the autogenous or reactive OCD group relied on clinical judgment regarding the predominant symptom profile. In participants with multiple symptom dimensions, classification was based on the symptom pattern that was most prominent, caused the greatest subjective distress, and had the greatest effect on daily functioning. However, interrater reliability for subtype assignment was not formally calculated, which may have introduced some degree of subjectivity into the classification process. In addition, the presence of mixed symptom profiles in a substantial proportion of the OCD sample suggests that differences in symptom content between groups should be interpreted in relation to the classification criteria rather than as wholly independent findings. Fourth, psychotropic medication use and psychiatric comorbidities may have influenced the results. Although treatment-related variables did not differ significantly between the reactive and autogenous OCD groups, antipsychotic use was numerically more common in the reactive group and may have affected RMET and Faux Pas performance. ADHD did not differ significantly between the OCD subgroups, but some anxiety-related comorbidities, particularly specific phobia and generalized anxiety disorder, were unevenly distributed. Because of the small subgroup sizes and low cell counts for several comorbidities, these variables were not included as covariates in the main analyses. Residual confounding related to medication status and psychiatric comorbidity therefore cannot be excluded. Fifth, IQ was not included as a covariate in the main analyses, although cognitive ability may influence performance on tasks such as the RMET and Faux Pas Test. Another limitation concerns the high overlap between Faux Pas Detection and Faux Pas Identification in the reactive OCD subgroup. Although the data and scoring were rechecked, the two subdomain scores were

identical in this subgroup, limiting their independent interpretation. Finally, multiple comparisons were conducted across clinical, metacognitive, and social cognition variables. Statistically significant findings, particularly those limited to a single social cognition subcomponent, should therefore be interpreted cautiously and require replication in larger samples.

CONCLUSION

The findings suggest that the autogenous–reactive distinction in adolescent OCD is reflected primarily in symptom content rather than in clearly differentiated metacognitive or social cognitive profiles. Although some metacognitive belief domains differed between the OCD groups and healthy controls, the reactive and autogenous OCD groups did not differ significantly from each other in metacognitive beliefs. Similarly, no significant group differences were observed in RMET or Faux Pas performance after correction for multiple comparisons. Correlation analyses revealed only selective associations between metacognitive beliefs and specific aspects of social understanding, particularly in the autogenous group. Overall, the autogenous–reactive distinction may be useful for characterizing symptom presentation but not for defining distinct metacognitive or social cognitive subtypes in adolescent OCD. Larger longitudinal studies are needed to clarify these relationships.

Ethical Approval: This study was approved by The Clinical Research Ethics Committee of Basaksehir Cam and Sakura City Hospital, (08.04.2025 KAEK-11/26.03.2025.116).

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Category 1	Concept/Design	O.G.
	Data acquisition	S.A.C., H.A., D.S.
	Data analysis/Interpretation	O.G.
Category 2	Drafting manuscript	O.G.
	Critical revision of manuscript	O.G.
Category 3	Final approval and accountability	O.G., S.A.C., D.S., H.A.
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RESEARCH ARTICLE

Neutrophils and leukocytes in acute ischemic stroke: Traditional markers for predicting clinical outcomes

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ABSTRACT

Objective: Systemic inflammation, particularly involving leukocytes and neutrophils, plays a critical role in stroke pathophysiology and lesion evolution and may influence treatment safety and outcomes. This study aimed to evaluate the prognostic value of admission leukocyte and neutrophil counts in patients with acute ischemic stroke treated with intravenous thrombolysis and/or mechanical thrombectomy.

Method: A total of 101 patients with ischemic stroke in the middle cerebral artery (MCA) territory who were treated with intravenous tissue plasminogen activator (IV tPA), mechanical thrombectomy (MT), or bridging therapy were analyzed. Demographic, clinical, laboratory, and neuroimaging data were collected. Infarct and hemorrhage volumes were calculated using the ABC/2 method. Clinical outcomes were assessed using National Institutes of Health Stroke Scale (NIHSS) scores and the modified Rankin Scale (mRS). Associations between inflammatory markers, radiological findings, hemorrhagic transformation, and functional outcomes were analyzed.

Results: Higher admission leukocyte and neutrophil counts were significantly associated with large artery atherosclerosis and were observed in patients undergoing mechanical thrombectomy or bridging therapy. Elevated leukocyte and neutrophil levels were associated with larger infarct volumes, an increased risk of intracranial hemorrhage, and poorer functional outcomes. Patients with unfavorable outcomes and those who died within 90 days had significantly higher leukocyte and neutrophil counts. Higher glycated hemoglobin (HbA1c) and C-reactive protein (CRP) levels and lower high-density lipoprotein (HDL) levels were associated with hemorrhagic transformation and poor prognosis. Successful recanalization was associated with smaller infarct volumes and better functional outcomes.

Conclusion: Admission leukocyte and neutrophil counts are associated with stroke etiology, hemorrhagic complications, and functional outcomes following reperfusion therapy. These readily available inflammatory biomarkers may serve as useful prognostic indicators in the management of acute ischemic stroke.

Keywords: Acute ischemic stroke, mechanical thrombectomy, intravenous thrombolysis, leukocyte, neutrophil

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INTRODUCTION

Acute ischemic stroke is a leading cause of mortality and long-term disability worldwide despite significant advances in reperfusion therapies. A substantial proportion of patients experience unfavorable outcomes, highlighting the need for readily available biomarkers that may assist in prognostic assessment and clinical decision-making.

Ischemic stroke triggers an acute inflammatory response characterized by the recruitment of various immune cells, particularly neutrophils and leukocytes, which play pivotal roles in disease pathophysiology (1). Elucidating the dynamics and behavior of these cells may enhance our understanding of the mechanisms underlying ischemia-related brain injury.

Following ischemic stroke, an inflammatory cascade is initiated in the brain, encompassing both local and systemic immune responses. Neutrophils are among the first immune cells to migrate into ischemic tissue, with evidence demonstrating their accumulation within the first 12 hours. This early neutrophil infiltration contributes significantly to secondary brain injury by promoting oxidative stress, releasing proinflammatory mediators, and disrupting the blood-brain barrier, thereby adversely affecting recovery (1–3). Neutrophils contribute to the early inflammatory response and become further activated during reperfusion after stroke, potentially contributing to the no-reflow phenomenon (2). This increased activation can intensify cerebral edema and exacerbate neuronal injury, highlighting the importance of the inflammatory process (4, 5).

Inflammatory markers are closely associated with the severity of ischemic stroke and subsequent clinical outcomes. Elevated leukocyte and neutrophil levels, in particular, have been associated with larger infarct volume, more severe initial neurological impairment, a greater likelihood of hemorrhagic transformation, and unfavorable clinical outcomes (3–6).

This study aimed to assess the relationship between admission leukocyte and neutrophil counts and radiological and functional outcomes in patients with acute ischemic stroke treated with intravenous tissue plasminogen activator (IV tPA) and/or mechanical thrombectomy. We examined the associations of these inflammatory markers with stroke etiology, hemorrhagic transformation, infarct volume, and 90-day functional outcomes to clarify their prognostic value in patients with acute ischemic stroke.

METHODS

Patient Selection

Patients admitted to the hospital with a diagnosis of acute ischemic stroke and treated with IV tPA and/or mechanical thrombectomy were included in the study. Based on the type of reperfusion therapy received, patients were categorized into three groups: those treated with IV tPA alone, those who underwent mechanical thrombectomy alone, and those who received bridging therapy, defined as mechanical thrombectomy following IV tPA administration. Only patients with acute ischemic stroke involving the middle cerebral artery territory were included. Ethical approval for this study was obtained from the Yeditepe University Clinical Research Ethics Committee (approval number: 1212). Written informed consent was obtained from the patients and/or their relatives.

Clinical Information and Neuroimaging

Demographic characteristics, including age and sex, were recorded. Detailed clinical data were collected, including baseline National Institutes of Health Stroke Scale (NIHSS) scores and the presence of comorbidities such as diabetes mellitus, hypertension, atrial fibrillation, and previous stroke. Laboratory parameters obtained at admission included complete blood count parameters (leukocyte and neutrophil counts), serum lipid profiles (low-density lipoprotein [LDL] and high-density lipoprotein [HDL]), glycated hemoglobin (HbA1c), and C-reactive protein (CRP) levels. To evaluate treatment time intervals, symptom-to-door, door-to-needle, symptom-to-puncture, and puncture-to-recanalization times were recorded.

Procedural data, including the number of passes, the method employed, and recanalization status according to the modified Thrombolysis in Cerebral Infarction (mTICI) score, were recorded.

Clinical outcomes were evaluated using NIHSS scores at 24 hours and at discharge and the modified Rankin Scale score at 90 days.

Stroke etiology was determined after etiological investigations according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.

The presence of intracranial hemorrhage after treatment was evaluated using cranial computed tomography (CT) according to the European Cooperative Acute Stroke Study (ECASS) criteria. Infarct volume was assessed using follow-up cranial magnetic resonance imaging (MRI) or CT obtained at least 24 hours after treatment. Infarct size was calculated

using the ABC/2 formula, where A represents the largest infarct diameter, B represents the diameter perpendicular to A, and C represents the number of imaging slices containing the infarct multiplied by the slice thickness. Infarct volume was then estimated as $A \times B \times C / 2$. Similarly, in patients with hemorrhagic transformation, intracranial hemorrhage volume was calculated using the same method on cranial CT images obtained at 24 hours.

Statistical Analysis

Statistical analyses were performed using appropriate parametric and nonparametric tests according to the distribution of the data. Nonparametric data were expressed as medians and interquartile ranges, whereas parametric data were expressed as means and standard deviations. Differences between groups were analyzed using Student's t-test or the Mann-Whitney U test, as appropriate, and correlation analyses were performed using Pearson's or Spearman's correlation tests. Fisher's exact test was used to evaluate categorical data. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 30.0.0 and GraphPad Prism version 9.1.2.

RESULTS

A total of 101 patients were enrolled in the study. Of these, 54 (53.5%) underwent mechanical thrombectomy, 31 (30.7%) were treated with IV tPA alone, and 16 (15.8%) received both IV tPA and mechanical thrombectomy (bridging therapy). Fifty-six (55.4%) patients were male and 45 (44.6%) were female. Twenty (19.8%) patients did not have a proximal occlusion, whereas 27 (26.7%) had an internal carotid artery (ICA) occlusion, 33 (32.7%) had a middle cerebral artery (MCA) M1 segment occlusion, and 21 (20.8%) had an MCA M2 segment occlusion (Table 1).

All patients underwent noncontrast cranial tomography on admission and at 24 hours. Baseline Alberta Stroke Program Early CT Scores (ASPECTS) ranged from 6 to 10. Overall, nine (8.9%) patients had an ASPECTS of 6, 27 (26.7%) had a score of 7, 25 (24.8%) had a score of 8, 32 (31.7%) had a score of 9, and eight (7.9%) had a score of 10.

The median leukocyte count was 8,355/ μ L (interquartile range [IQR]: 6,582.5–10,697.5) in the overall study population, 6,980/ μ L (IQR: 6,020–9,470) in the IV tPA group, 9,060/ μ L (IQR: 6,590–11,030) in

the mechanical thrombectomy group, and 9,125/ μ L (IQR: 7,067.5–10,847.5) in the bridging therapy group. The median neutrophil count and neutrophil percentage were 4,060/ μ L (IQR: 3,120–6,390) and 61.0%, respectively, in the IV tPA group; 6,270/ μ L (IQR: 4,060–8,455) and 68.3%, respectively, in the mechanical thrombectomy group; and 5,880/ μ L (IQR: 4,585–7,105) and 65.9%, respectively, in the bridging therapy group. Both neutrophil count and neutrophil percentage differed significantly among the treatment groups ($p=0.007$ and $p=0.003$, respectively) (Fig. 1a, b), with patients treated with mechanical thrombectomy having significantly higher neutrophil counts and percentages than those treated with IV tPA alone. To assess whether infection might account for the differences in neutrophil counts, CRP levels were compared among the groups; no significant difference was observed ($p=0.089$).

Successful recanalization was achieved in 55 (78.6%) patients who underwent mechanical thrombectomy (MT), including 42 (77.8%) in the MT-alone group and 13 (81.3%) in the bridging therapy group (Fig. 2a).

According to the TOAST classification, 23 (22.8%) patients had large artery atherosclerosis, 44 (43.6%) had cardioembolism, and 14 (13.9%) had small vessel disease. Four (4%) patients had other determined etiologies, such as vasculitis, and 16 (15.8%) were classified as having cryptogenic stroke. Analysis of the relationship between leukocyte and neutrophil counts and stroke etiology revealed that patients with large artery atherosclerosis had significantly higher leukocyte and neutrophil numbers than patients with other etiologies ($p=0.004$ and $p=0.006$, respectively).

The median lesion volume at 24 hours was 3,857.68 mm^3 (IQR: 1,322.19–35,372.16) in the IV tPA group, 106,375.61 mm^3 (IQR: 20,674.22–218,992.67) in the mechanical thrombectomy group, and 42,654.81 mm^3 (IQR: 11,903.33–106,176.53) in the bridging therapy group. Seventy-five (74.3%) patients had no intracranial hemorrhage. Intracranial hemorrhage was observed in three (9.7%) patients in the IV tPA group, 18 (33.3%) in the MT group, and five (31.3%) in the bridging therapy group. Lesion volume differed significantly among the treatment groups ($p<0.001$), with patients undergoing mechanical thrombectomy having significantly larger lesion volumes than those treated with IV tPA alone. Hemorrhage volume also differed significantly among the groups ($p=0.044$), with greater hemorrhage volumes observed in the mechanical thrombectomy group than in the IV tPA group.

Table 1: Patient characteristics according to treatment group

	IV tPA (n=31)	MT (n=54)	Bridging therapy (n=16)	Total (n=101)	p
Demographic characteristics					
Age (mean±SD)	66.1±14.8	67.2±13.1	62.3±15.2	66.1±13.9	0.52
Female sex, n (%)	14 (45.2)	26 (48.1)	5 (31.3)	45 (44.6)	0.49
Medical history					
Diabetes mellitus, n (%)	15 (48.4)	19 (35.2)	7 (43.8)	41 (40.6)	0.47
Hypertension, n (%)	22 (71)	32 (59.3)	10 (62.5)	64 (63.4)	0.56
Hyperlipidemia, n (%)	22 (71)	30 (55.6)	10 (62.5)	62 (61.4)	0.37
Atrial fibrillation, n (%)	9 (29)	25 (46.3)	4 (25)	38 (37.6)	0.15
Previous stroke, n (%)	9 (29)	12 (22.2)	1 (6.3)	22 (21.8)	0.08
Smoking, n (%)	7 (22.6)	7 (13)	4 (25)	18 (17.8)	0.38
Clinical characteristics					
Baseline NIHSS score (median, IQR)	6 (4-9)	13 (11-15.25)	9.5 (7-12.75)	11 (7-14)	0.001
Occlusion site					
ICA	1 (3.2)	21 (38.9)	5 (31.3)	27 (26.7)	0.015
M1 segment	–	27 (50)	6 (37.5)	33 (32.7)	
M2 segment	10 (32.3)	6 (11.1)	5 (31.3)	21 (20.8)	
Symptom-to-door time (median, IQR)	70.5 (52.5-118)	137.5 (50-283.25)	61 (40-87)	90 (50-202)	0.015
Door-to-needle time (median, IQR)	79 (59-100)	–	72 (64.5-86)	73 (61-95)	0.47
Symptom-to-puncture time (median, IQR)	–	313.5 (195-420)	177 (146-235)	240 (177-363)	0.001
Puncture-to-recanalization time (median, IQR)	–	28 (20-51.5)	30 (14.25-62.75)	28.5 (19.5-59)	0.9
Interventional procedures					
Technique employed					0.42
Stent retriever, n (%)	–	25 (47.2)	9 (56.3)	34 (49.3)	0.97
Aspiration, n (%)	–	19 (35.8)	3 (18.8)	22 (31.9)	
Combined, n (%)	–	9 (17)	4 (25)	13 (18.8)	
Number of passes (median, IQR)	–	1 (1-3)	1.5 (1-2.75)	1 (1-3)	0.97
Recanalization score					0.53
mTICI 0-2a	–	12 (22.3)	3 (18.8)	15 (21.4)	0.003
mTICI 2b-3	–	42 (77.7)	13 (81.2)	55 (78.6)	
Clinical outcomes					
NIHSS score at 24 hours (median, IQR)	4 (3-7)	10.5 (7.75-14)	7 (4-14)	8 (4-12.5)	<0.001
NIHSS score at discharge (median, IQR)	3 (0-5.25)	8 (4-13)	6 (3-9)	5 (2-11)	<0.001
mRS score at 90 days					0.003
mRS 0-2	24 (77.4)	22 (40.7)	5 (31.3)	51 (50.5)	0.003
mRS 3-5	5 (16.1)	16 (29.7)	8 (50)	29 (28.7)	
mRS 6	2 (6.5)	16 (29.6)	3 (18.8)	21 (20.8)	

SD: Standard deviation; IQR: Interquartile range; ICA: Internal carotid artery.

Leukocyte and neutrophil counts differed significantly between patients with and without intracranial hemorrhage ($p=0.022$ and $p=0.029$, respectively) (Fig. 1c, d). Higher leukocyte and neutrophil counts were associated with intracranial hemorrhage. HbA1c levels showed a similar

association ($p=0.04$). Patients with higher HDL levels had a lower frequency of intracranial hemorrhage at 24 hours ($p=0.021$), whereas LDL levels did not differ significantly ($p=0.27$). Similar findings were observed in the subgroup of patients who underwent mechanical thrombectomy and achieved successful

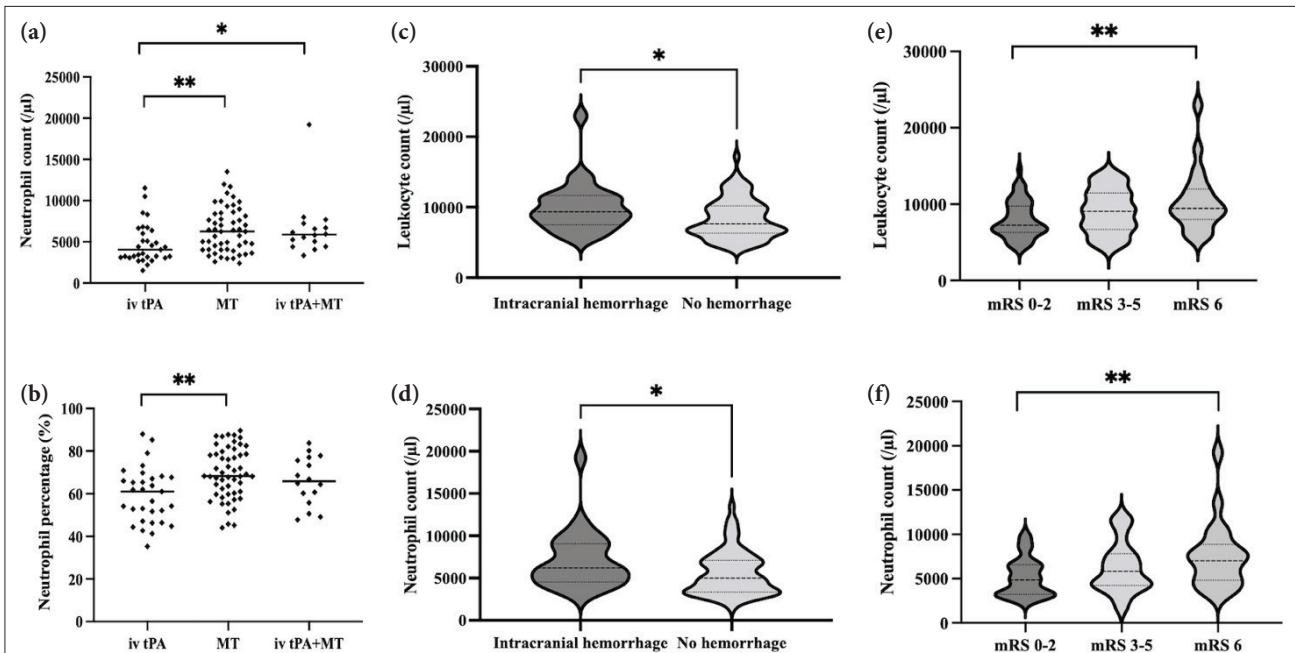


Figure 1. Neutrophil and leukocyte profiles according to treatment, hemorrhagic transformation, and functional outcome. Neutrophil count and ratio were higher in the mechanical thrombectomy and bridging therapy groups than in the intravenous tissue plasminogen activator (IV tPA) group ($p=0.007$ and $p=0.003$, respectively) (a, b). Leukocyte and neutrophil counts were higher in patients with intracranial hemorrhage at 24 hours ($p=0.022$ and $p=0.029$, respectively) (c, d) and in patients with poor functional outcomes at 90 days ($p=0.019$ and $p=0.008$, respectively) (e, f).

recanalization. In this subgroup, leukocyte and neutrophil counts, HDL cholesterol levels, and HbA1c levels differed significantly between patients with and without intracranial hemorrhage ($p=0.026$, $p=0.041$, $p=0.009$, and $p=0.046$, respectively).

The modified Rankin Scale (mRS) was used to assess functional outcomes during follow-up. Patients with mRS scores of 0–2 were considered functionally independent. At 90 days, 51 (50.5%) patients achieved functional independence (mRS 0–2), including 24 (77.4%) in the IV tPA group, 22 (40.7%) in the mechanical thrombectomy group, and five (31.3%) in the bridging therapy group. Twenty-one (20.8%) patients had died by 90 days (Fig. 2b).

Lesion and hemorrhage volumes at 24 hours differed significantly according to functional independence ($p<0.001$ and $p=0.003$, respectively). Hemorrhage volume was significantly greater in patients with an mRS score of 6. Functionally independent patients had smaller lesion volumes at 24 hours. Patients with a favorable functional outcome (mRS 0–2) demonstrated a significantly greater reduction in NIHSS score from baseline to 24 hours after treatment ($p=0.002$).

Leukocyte and neutrophil counts differed significantly among the 90-day functional outcome

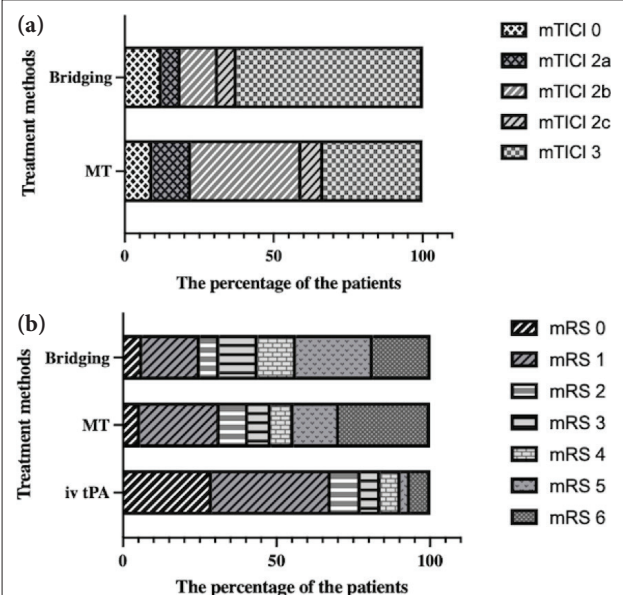


Figure 2. Recanalization scores and clinical outcomes. Modified Thrombolysis in Cerebral Infarction (mTICI) scores (a) and modified Rankin Scale (mRS) scores (b) of patients at 90 days according to treatment method.

groups ($p=0.019$ and $p=0.008$, respectively), with the highest values observed in patients with an mRS score of 6 at 90 days (Fig. 1e, f). In addition, CRP,

HDL cholesterol, and HbA1c levels were significantly associated with functional outcomes ($p=0.017$, $p=0.020$, and $p=0.020$, respectively). Higher CRP and HbA1c levels, together with lower HDL cholesterol levels, were associated with unfavorable functional outcomes.

Recanalization status, determined using the mTICI scoring system, was associated with lesion volume at 24 hours ($p=0.033$); patients with successful recanalization (mTICI 2b–3) had smaller lesions at 24 hours. Recanalization status was also significantly associated with the 90-day mRS score ($p=0.041$), with unsuccessful recanalization being associated with poorer functional outcomes.

DISCUSSION

This study examined the associations between inflammatory biomarkers and clinical outcomes in patients with acute ischemic stroke undergoing intravenous thrombolysis and/or mechanical thrombectomy. Our results demonstrated that admission leukocyte and neutrophil counts were associated with stroke etiology, hemorrhagic transformation, and functional outcomes, highlighting the role of systemic inflammation in stroke pathophysiology and prognosis following reperfusion therapy.

Patients undergoing mechanical thrombectomy or bridging therapy had significantly higher leukocyte and neutrophil counts than those treated with IV tPA alone. CRP levels did not differ significantly among the treatment groups, suggesting that infection was unlikely to account for the observed differences. In addition, none of the patients included in the study had a hematological disorder known to alter complete blood count parameters. These findings may reflect differences in underlying stroke severity, as patients treated with mechanical thrombectomy typically have large vessel occlusions and more extensive ischemic injury. Consistent with this interpretation, previous studies have demonstrated that elevated leukocyte and neutrophil counts at admission are strongly associated with the presence of large vessel occlusion (7). Moreover, lymphocyte counts and ratios have been shown to predict large vessel occlusion in acute ischemic stroke (8).

Patients with large artery atherosclerosis had higher leukocyte and neutrophil counts than those with other stroke etiologies. Large artery atherosclerosis is characterized by persistent

vascular inflammation and unstable atherosclerotic plaques, conditions that may predispose patients to an amplified inflammatory response during acute ischemia (4). Higher levels of systemic inflammatory markers, particularly leukocyte counts, have been associated with an increased risk of cerebrovascular disease, including acute ischemic stroke resulting from atherosclerosis (9). These findings underscore the important role of inflammation in the development of atherosclerosis and subsequent vascular occlusion. Our results further support existing evidence that the systemic inflammatory burden varies among stroke subtypes and may affect both therapeutic response and clinical outcomes.

Hemorrhagic transformation is one of the most feared complications of reperfusion therapy. In this study, higher leukocyte and neutrophil counts were significantly associated with intracranial hemorrhage at 24 hours. Considering the potential effect of recanalization on hemorrhagic transformation, subgroup analyses were performed in patients who underwent mechanical thrombectomy and achieved successful recanalization. The associations persisted in this subgroup, suggesting that inflammation may be associated with hemorrhagic risk independently of angiographic reperfusion. Both experimental and clinical studies have demonstrated that neutrophil-driven inflammatory processes, together with endothelial injury, proteolytic enzyme release, and oxidative stress, can increase vascular permeability and thereby promote hemorrhagic transformation (1, 4). Moreover, admission and postprocedural neutrophil-to-lymphocyte ratios have been identified as independent prognostic factors for intracranial hemorrhage and functional outcomes in patients with large vessel occlusion (6, 10–12).

Functional outcome at 90 days, assessed using the modified Rankin Scale, was significantly associated with leukocyte and neutrophil counts. Patients who died had the highest leukocyte and neutrophil levels, whereas those who achieved functional independence had lower counts and showed greater early neurological improvement, as reflected by a larger reduction in NIHSS scores. Consistent with these findings, previous clinical studies have reported that elevated leukocyte and neutrophil counts in acute ischemic stroke are associated with larger infarct volumes and poorer functional outcomes (13–16). Neutrophils are among the first immune cells recruited to ischemic brain tissue and are known to promote blood-brain

barrier disruption, microvascular impairment, and secondary neuronal injury, which may account for their association with poorer radiological and clinical outcomes (4).

Moreover, elevated HbA1c levels were associated with an increased risk of hemorrhage, suggesting that poor long-term glycemic control may compromise microvascular integrity. In contrast, higher HDL levels were associated with a lower risk of hemorrhagic complications, potentially because of their anti-inflammatory and endothelial-protective effects. Additionally, increased CRP and HbA1c levels, together with reduced HDL levels, were associated with poorer functional outcomes, underscoring the complex interplay among inflammation, metabolic status, and stroke recovery.

Recent evidence indicates that higher HbA1c levels are associated with an increased risk of poor functional recovery and higher mortality in patients with acute ischemic stroke (17, 18). HbA1c reflects chronic glycemic status and may therefore provide important information regarding long-term outcomes (19). Accordingly, patients with poor prestroke glycemic control may experience worse neurological outcomes. HDL modulates macrophage and adipocyte function through cholesterol transport mechanisms, thereby exerting anti-inflammatory and antiatherosclerotic effects (20, 21). In acute ischemic stroke, the neutrophil-to-HDL cholesterol ratio (NHR) has been identified as a potential prognostic marker, with an elevated NHR associated with poor functional outcomes in patients treated with either intravenous thrombolysis or mechanical thrombectomy (22, 23).

Successful recanalization was associated with smaller infarct volumes and better functional outcomes, emphasizing that timely and effective reperfusion remains a key prognostic factor (24). Lesion volume at 24 hours was closely associated with both hemorrhagic transformation and functional outcome. Larger lesion volumes were associated with an increased risk of hemorrhagic complications and poorer clinical outcomes, as previously reported in the literature (25).

Although neutrophil and leukocyte counts have been extensively investigated in acute ischemic stroke, the present study extends previous work in several important ways. Specifically, it examines acute reperfusion therapies across defined patient subgroups, provides a detailed analysis of radiological

parameters, including lesion volume, hemorrhage volume, and reperfusion scores, and simultaneously evaluates additional laboratory markers such as HbA1c and CRP.

This study has several limitations. First, as a single-center study, the findings may not be fully generalizable to broader patient populations. The relatively modest sample size, particularly within the treatment subgroups, may have limited the statistical power to detect smaller differences and conduct more detailed subgroup analyses. Finally, only admission leukocyte and neutrophil counts were evaluated; serial measurements and additional inflammatory biomarkers might have provided a more comprehensive assessment of the temporal inflammatory response.

Our results indicate that systemic inflammation, particularly neutrophil-mediated responses, is associated with the safety and functional outcomes of reperfusion treatment for acute ischemic stroke. These findings suggest that leukocyte and neutrophil counts, which are routinely available in clinical practice, may serve as useful prognostic indicators. A better understanding of inflammatory mechanisms, particularly those involving neutrophils, may contribute to the development of future therapeutic strategies aimed at modulating the immune response and potentially improving outcomes in patients with ischemic stroke.

Ethical Approval: This study was approved by The Yeditepe University Clinical Research Ethics Committee with approval number 1212, date: 07.05.2020.

Informed Consent: Written informed consent was obtained from all participants.

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Contribution Categories		Author Initials
Category 1	Concept/Design	S.A., B.Y., Y.G.O.
	Data acquisition	S.A.
	Data analysis/Interpretation	S.A., B.Y.
Category 2	Drafting manuscript	S.A.
	Critical review or revision of manuscript	B.Y., Y.G.O.
Category 3	Final approval and accountability	S.A., B.Y., Y.G.O.
Other	Supervision	Y.G.O., B.Y.

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RESEARCH ARTICLE

Peroneal neuropathy with foot drop after bariatric surgery: A neurosurgical perspective

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ABSTRACT

Objective: Peroneal neuropathy is the most common entrapment neuropathy of the lower extremity and most commonly results from compression of the peroneal nerve at the fibular head. This study aimed to evaluate the relationship between peroneal neuropathy and rapid weight loss after bariatric surgery and to assess the outcomes of surgical decompression in patients presenting with foot drop.

Method: Between 2020 and 2025, five patients underwent surgical treatment for foot drop due to peroneal neuropathy following bariatric surgery. The diagnosis was confirmed by clinical evaluation, imaging, and electromyography (EMG). Changes in body weight and body mass index before and after bariatric surgery, the duration of weight loss, time to onset of clinical symptoms, and changes in clinical findings after peroneal nerve decompression were evaluated.

Results: Of the five patients who developed peroneal neuropathy after bariatric surgery, two were female and three were male. The mean age was 37 years. Compared with preoperative body weight, the mean weight reduction was 36.6%. Patients experienced the greatest weight loss within the first 4–6 months after bariatric surgery. Foot weakness developed a mean of 7.2 months after bariatric surgery. All patients underwent peroneal nerve decompression. At the six-month follow-up, four patients had a Medical Research Council (MRC) score of 5, including one patient with bilateral involvement, whereas one patient had an MRC score of 4.

Conclusion: Both mechanical and metabolic factors may contribute to the development of peroneal neuropathy after rapid and substantial weight loss. Given the increasing prevalence of obesity, the growing use of bariatric surgery, and changing societal attitudes toward weight loss, clinicians should remain alert to such neurological complications. Early diagnosis and timely surgical intervention may contribute to favorable neurological outcomes.

Keywords: Bariatric surgery, peroneal neuropathy, foot drop, surgical decompression

INTRODUCTION

Peroneal neuropathy is the most common entrapment neuropathy of the lower extremity. It is also the third most common focal neuropathy in adults and accounts

for approximately 15% of all mononeuropathies, after median and ulnar neuropathies (1). Peroneal neuropathy may cause complete or partial foot drop and may be accompanied by sensory impairment. Pain may occur in some conditions, such as traumatic

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injuries or compressive lesions, but it is not a typical presenting symptom. Trauma, compression, iatrogenic injury, and medical or metabolic disorders are among the etiological factors associated with peroneal neuropathy, with compression being the most common. The common peroneal nerve branches from the sciatic nerve, courses around the neck of the fibula, and subsequently divides into its terminal branches supplying the lower leg and foot. Compression may occur anywhere along the course of the nerve but is most common at the fibular head, where the nerve is superficial and covered by only a thin layer of subcutaneous tissue (2). Both conservative and surgical treatment options may be considered for foot drop associated with peroneal neuropathy. Conservative treatment is generally considered initially in selected patients (3).

Peroneal neuropathy has also been reported as a neurological complication following bariatric surgery. Bariatric surgery encompasses a range of procedures designed to achieve weight loss. These procedures alter gastrointestinal anatomy to restrict food intake and, in some cases, modify nutrient absorption and metabolism, thereby promoting weight loss. Loss of the protective fat pad surrounding the fibular head may predispose the common peroneal nerve (CPN) to compression, resulting in peroneal neuropathy and associated neurological symptoms. This condition, sometimes referred to as "slimmer's paralysis," describes peroneal neuropathy associated with excessive and rapid weight loss (4–7).

In this study, we present our clinical experience with patients who developed peroneal neuropathy following bariatric surgery and examine its association with postoperative weight loss.

METHODS

Data were processed using Microsoft Excel. Demographic characteristics, mean values, and standard deviations were calculated. Changes in body weight over time and body mass index (BMI) were also evaluated. No inferential statistical analyses were performed; only descriptive analyses were conducted.

Between 2020 and 2025, five of 30 patients who presented to our clinic with foot drop had a history of bariatric surgery. All patients underwent clinical examination, laboratory evaluation, and radiological imaging. Laboratory parameters, including vitamin B12, folate, thiamine (vitamin B1), vitamin E, and copper levels, were reviewed, and clinically relevant

abnormalities were identified. Magnetic resonance imaging (MRI) was performed to visualize the peroneal nerve at the level of the fibular head and to exclude other potential causes of foot drop, including ganglion cysts, intraneural cysts, tumors, and other space-occupying lesions. Electromyography examinations were performed in all patients. Muscle strength was assessed using the Medical Research Council (MRC) scale (8). Clinical examination, electrophysiological findings, laboratory results, and imaging supported the diagnosis of foot drop associated with peroneal neuropathy. All patients were subsequently evaluated by a neurologist. Peroneal nerve decompression was performed in patients for whom surgical treatment was considered appropriate.

Surgical Procedure

The procedure was performed under local or general anesthesia. The knee was placed in slight flexion, and the lateral aspect of the knee was prepared according to standard sterile surgical technique. The fibular head was identified and marked, and a curved incision extending proximally and distally from this landmark was planned. After incision of the skin and subcutaneous tissue, the common peroneal nerve was carefully exposed at the level of the popliteal fossa and dissected distally. The fascia overlying the peroneus longus muscle was identified, and fasciotomy was performed at the level of the fibular head. The superficial and deep peroneal branches were subsequently identified and decompressed (Fig. 1).

RESULTS

Of the five patients who developed peroneal neuropathy following bariatric surgery, two were female and three were male. The mean age was 37 years. Three patients had right-sided entrapment, one had left-sided entrapment, and one had bilateral clinical involvement. After the onset of foot drop, all patients underwent electromyography (EMG). Electrophysiological findings included partial axonal injury involving the right deep peroneal branch in one patient, axonal injury of the right peroneal nerve in another, and conduction block of the left peroneal nerve at the fibular head in a third patient. In one patient, conduction block and reduced conduction velocity were detected at the knee level in both peroneal nerves. In another patient, bilateral peroneal nerve motor conduction blocks consistent with entrapment neuropathy were detected at the level of

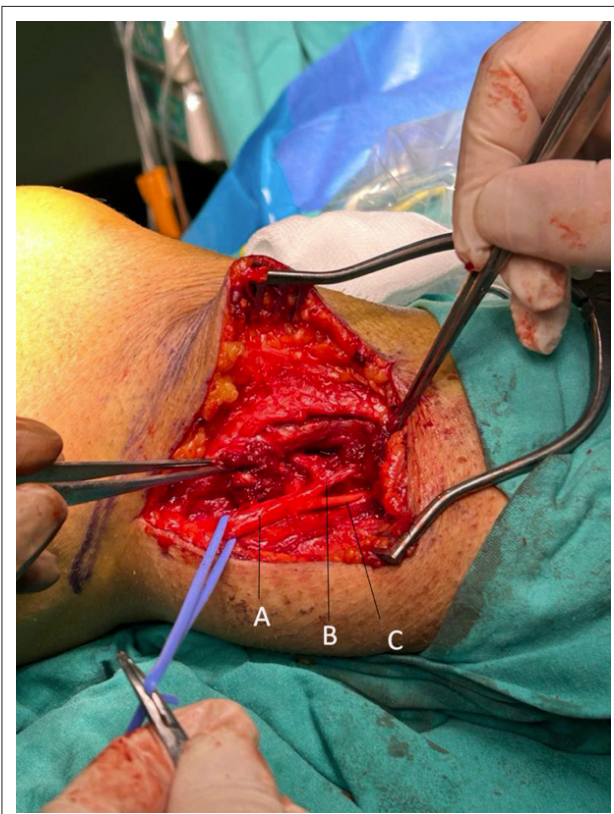


Figure 1. Surgical exposure of the right peroneal nerve. (a) Common peroneal nerve. (b) Deep peroneal nerve. (c) Superficial peroneal nerve.

the fibular heads. Although two patients demonstrated bilateral electrophysiological abnormalities, only one had bilateral foot drop (Fig. 2). Compared with pre-bariatric surgery body weight, the mean reduction in body weight was 36.6%. The mean monthly weight loss from bariatric surgery to the onset of foot drop was 7.4 kg/month. The greatest weight reduction

occurred during the first 4–6 months after bariatric surgery. Foot weakness developed a mean of 7.2 months after bariatric surgery. The mean reduction in BMI was 36.9% compared with the preoperative value, assessed after a mean postoperative period of 4.6 months, when substantial weight loss had become evident. The mean interval during which patients experienced symptoms suggestive of peroneal nerve entrapment, such as sensory loss, tingling, or weakness of the foot or ankle, before the development of foot drop was 7.2 months (range, 5–9 months). Patients presented to our clinic a mean of 7.2 days (range, 5–9 days) after the onset of foot drop (Table 1).

At the 15-day follow-up after decompression surgery, the MRC score improved from 1 to 2 in one patient and from 0 to 1 in three patients. In the patient with bilateral peroneal nerve compression, decompression procedures were performed two weeks apart. In this patient, the MRC score improved from 0 to 1 on the right side and from 2 to 3 on the left side. At the six-month follow-up, four patients had achieved an MRC score of 5, including the patient with bilateral involvement, whereas one patient had an MRC score of 4.

DISCUSSION

This study evaluated patients who developed peroneal neuropathy and foot drop following bariatric surgery, focusing on the magnitude and duration of weight loss and the role of peroneal nerve decompression in treatment.

In 1929, Woltman was the first to describe an association between substantial weight loss and foot drop. Later, in 1947, Nagler et al. (9) reported a case

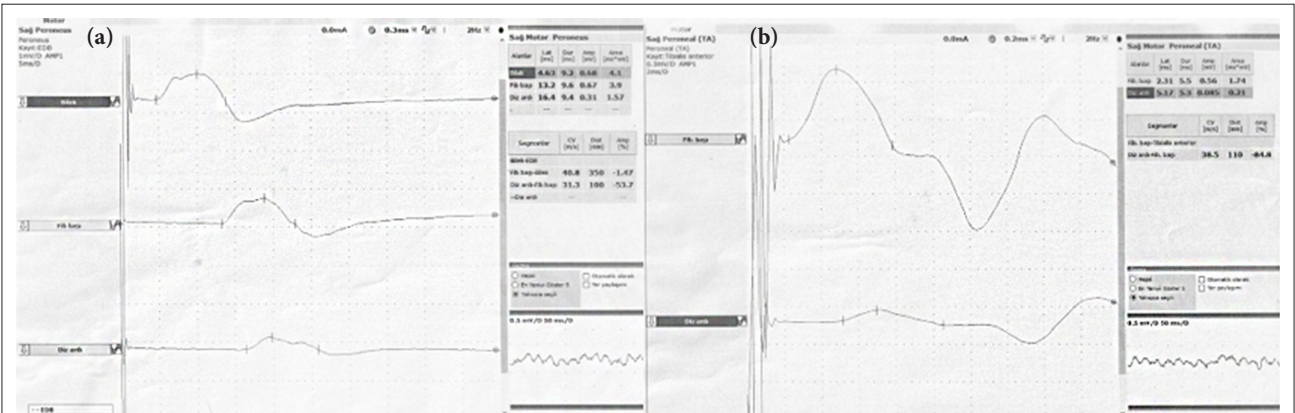


Figure 2. Electromyography (EMG) tracings demonstrating right peroneal neuropathy. (a) Recording site: extensor digitorum brevis muscle. (b) Recording site: tibialis anterior muscle.

Table 1: Demographic and clinical characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Mean	Range	SD
Sex	Male	Male	Female	Male	Female			
Age, years	49	43	34	27	37	37	27-49	7.9
Preoperative weight	163	180	150	140	104	147.4	104-180	25.5
Postoperative weight	100	122	103	81	64	94	81-122	19.8
Weight loss	63 (38.6%)	58 (32.2%)	47 (31.3%)	59 (42.1%)	40 (38.5%)	53.4 (36.6%)	40-63	4.1
Preoperative BMI	53.2	54.3	62.4	46.8	34	50.4	34-62.4	9.5
Postoperative BMI	32.7	36.8	42.9	27.1	20.9	32.1	20.9-42.9	7.6
Reduction in BMI (%)	38.5	32.2	31.2	42.1	40.6	36.9	31.2-42.1	4.4
Duration of weight loss (months)	4	4	4	5	6	4.6	4-6	
Time from surgery to symptom onset (months)	6	5	8	8	9	7.2	5-9	
Time from foot-drop onset to presentation (days)	5	9	6	8	8	7.2	5-9	
Affected side	Right	Right	Left	Bilateral	Right			
Preoperative MRC grade	1	0	0	R: 0; L: 2	0			
MRC grade at 6 months	5	5	5	R: 5; L: 5	4			

BMI: Body mass index; MRC: Medical Research Council; SD: Standard deviation.

of peroneal neuropathy in which weight loss was also considered a contributing factor (9–11). Since then, numerous studies have addressed this relationship, and weight loss has become a well-recognized risk factor for peroneal neuropathy. Weight loss has been reported as an etiological factor in up to 15% of patients with peroneal neuropathy (12). Nevertheless, the exact pathophysiological mechanisms remain incompletely understood.

In addition to the proposed role of reduced protective adipose tissue at the fibular head in the development of peroneal neuropathy and foot drop after bariatric surgery, Lale et al. (12) histopathologically demonstrated fibrotic changes in the fascia surrounding the peroneal nerve following excessive weight loss. Enlargement of blood vessels and inflammatory infiltration within the fascia were interpreted as evidence of a chronic process that may increase the nerve's susceptibility to compression (12). Mechanical irritation related to instability or hypermobility of the proximal tibiofibular joint may also increase the vulnerability of the peroneal nerve (13).

Mechanical factors, however, may not be the only contributors. The pathogenesis of peroneal neuropathy associated with marked weight loss is probably multifactorial, and metabolic factors may also contribute to nerve dysfunction. Thaisethawatkul et al. (14) investigated neuropathies associated with bariatric surgery and suggested that malnutrition may represent an important risk factor. Sural nerve biopsy findings in their study demonstrated prominent axonal degeneration and perivascular inflammation, suggesting that inflammatory and immune-mediated mechanisms may also contribute to the pathogenesis of peroneal neuropathy (14). Weyns et al. (10) proposed that that nerve edema may contribute to the development of compression neuropathy, in a manner analogous to mechanisms implicated in diabetic neuropathy. This intraneural edema may result from metabolic disturbances, such as hypoalbuminemia with reduced oncotic pressure or intracellular sorbitol accumulation causing osmotic stress, and may contribute to nerve dysfunction, particularly at anatomically vulnerable entrapment sites (10).

Weight Loss and Changes in BMI

Previous studies have emphasized the relationship between substantial weight loss and peroneal nerve entrapment. Margulis et al. (5) reported bilateral peroneal entrapment neuropathy in a patient who lost 40 kg following a strict diet. Elias et al. (15) described a patient who lost 39.5 kg after bariatric surgery and

subsequently developed peroneal neuropathy. In the study by Lale et al. (12), the mean weight loss over a six-month period was 68.74 kg.

In our series, the mean weight loss was 53.4 kg, corresponding to a 36.6% reduction in body weight at the onset of symptoms of peroneal entrapment neuropathy. Similarly, the mean reduction in BMI following bariatric surgery was 36.9%.

Duration and Rate of Weight Loss

In the study by Lale et al. (12), the reported mean monthly weight loss was 11.46 kg/month. In a review by Fares et al. (16) that included nine studies, the duration of weight loss ranged from 2 to 18 months among 21 patients who underwent bariatric surgery. Elias et al. (15) reported a six-month period of weight loss in a patient who developed peroneal neuropathy after bariatric surgery. Weyns et al. (10) compared patients who developed foot drop with those who did not and found that the mean duration of weight loss was 8.6 months in patients who developed foot drop and 21.7 months in those who did not. According to Weyns et al. (10), rapid weight loss may be associated with the development of foot drop.

In our study, the mean period during which substantial postoperative weight loss occurred was 4.6 months. The mean monthly weight loss from bariatric surgery to the onset of peroneal neuropathy symptoms was 7.4 kg/month. These observations suggest that not only the magnitude of weight loss but also its rapidity may contribute to the development of peroneal neuropathy. Our findings are consistent with those of previous studies. The substantial reduction in body weight (36.6%) over a relatively short period of 4.6 months suggests that both the magnitude and rapidity of weight loss may have contributed to the development of foot drop. Although these findings are consistent with previous reports, the small sample size of our study necessitates further investigation in larger cohorts.

Importance of the Ratio

While the standard deviations of the pre- and postoperative weight values were relatively large, the standard deviations of the changes in weight and BMI were 4.1 and 4.4, respectively, providing measurable data on the relationship between these changes and the development of the clinical picture. In other words, the rate of weight and BMI reduction may be more relevant to the development of the clinical picture than the absolute amount of weight loss. Although the magnitude of weight loss may still be important, our findings suggest that its relative contribution may be less prominent.

Treatment Options

Several studies have reported improvement in neurological symptoms with conservative management, including nutritional support, stabilization of weight loss, and physical therapy (6, 17). In contrast, Elias et al. (15) emphasized that surgical decompression may be indicated in patients with acute, severe, or persistent neurological deficits. At present, however, there is no consensus regarding the optimal selection or timing of conservative versus surgical treatment.

Oosterbos et al. (18), in a survey of specialists regarding the management of peroneal nerve entrapment and foot drop, reported that 78% of respondents believed that the available literature was insufficient to guide treatment and that additional research, including randomized controlled trials, was needed. Most specialists considered neurolysis a valid treatment option for patients with persistent foot drop. Although approximately 90% preferred surgical treatment within six months after symptom onset, there was no consensus regarding the optimal timing of surgery, and approximately one-fifth favored surgical intervention as soon as possible after diagnosis (18).

In our clinic, surgical decompression was selected for all five patients presenting with foot drop and was performed within 5–9 days after presentation. In the patient with bilateral peroneal neuropathy, decompression of the contralateral side was performed two weeks after the first procedure. Following surgery, all patients were referred for physical therapy and rehabilitation.

Selection of a Functional Outcome Measure

In the survey conducted by Oosterbos et al. (18), postoperative recovery was evaluated using several different methods. Thirty-six percent of physicians focused primarily on recovery of walking ability, 32% assessed ankle dorsiflexion strength using the MRC scale, 20% relied on patient-reported recovery, and 10% assessed electrophysiological changes (18).

In our study, late postoperative electrophysiological follow-up data were not available. Therefore, the MRC scale was used as the principal measure of neurological recovery. Based on our literature review, we selected this method because this scoring system remains valid and is currently in use.

Study Limitations

Although no significant abnormalities were observed in the laboratory values of these five patients with foot drop, further studies are needed to investigate other factors that may have contributed to the development

of these symptoms. A comparative study including patients undergoing conservative treatment could also be conducted. However, the number of patients in the present study was insufficient for such a comparison, and such an evaluation would require a prospective design. In addition, monitoring electrophysiological changes during follow-up could have provided valuable data; however, the inability to contact the patients during the subsequent follow-up period prevented such monitoring.

CONCLUSION

Peroneal neuropathy should be considered an important cause of foot drop in neurosurgical practice. Early diagnosis and timely initiation of treatment through appropriate medical history, physical and neurological examinations, and imaging are important. In patients with EMG-confirmed peroneal neuropathy, a history of recent rapid or substantial weight loss should be specifically investigated, including a history of bariatric surgery. In recent years, the prevalence of obesity has increased worldwide (19). Bariatric surgery has become an important treatment option for obesity. Bariatric surgeons and dietitians should remain vigilant for potential neurological complications during postoperative follow-up, while neurosurgeons should consider a history of bariatric surgery and associated weight loss when evaluating the etiology of conditions such as peroneal neuropathy.

Ethical Approval: This study was approved by The Biruni University Scientific Research Ethics Committee (Decision No: 2025-BiAEK/03-24 Date: 24.03.2025).

Informed Consent: Written informed consent was obtained from all participants.

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	Data analysis/Interpretation	I.A., O.E.S., C.O.
Category 2	Drafting manuscript	I.A., B.K., F.M.K., O.E.S.
	Critical revision of manuscript	H.B.G., E.E., C.O.
Category 3	Final approval and accountability	H.B.G., O.E.S., I.A., C.O., B.K., F.M.K., E.E.
Other	Supervision	E.E., H.B.K., C.O.

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RESEARCH ARTICLE

Symptom predominance, treatment delay, and four-year remission outcomes in first-episode schizophrenia: A single-center cohort from Türkiye

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ABSTRACT

Objective: This study aimed to estimate the rate and baseline predictors of symptomatic remission and to examine the association between symptom predominance during the untreated psychosis period and its duration in a diagnostically homogeneous cohort of individuals with first-episode schizophrenia treated under routine clinical conditions in Türkiye.

Method: This retrospective cohort study included 84 inpatients admitted with first-episode psychosis between 2020 and 2022 who subsequently received a longitudinally confirmed diagnosis of schizophrenia. Patients with affective, substance-induced, organic, or peripartum psychoses were systematically excluded. Follow-up assessments were completed for 39 participants (46.4%) after a mean follow-up of 48.5 months. Cross-sectional symptomatic remission was assessed according to the severity component of the Remission in Schizophrenia Working Group criteria using the eight specified Positive and Negative Syndrome Scale (PANSS) items. Exploratory associations between selected baseline variables and remission were examined using binomial logistic regression, and the association between symptom predominance (positive vs. negative) during the untreated psychosis period and duration of untreated psychosis (DUP) was examined in the full baseline cohort.

Results: At follow-up, 71.8% (28/39; 95% confidence interval, 56.2%–83.5%) of the 39 assessed participants met the symptomatic remission criterion. Remitters had a significantly older age at illness onset and shorter DUP than non-remitters; current living arrangement and medication adherence also differed significantly between groups. An exploratory multivariable logistic regression model including age at illness onset, sex, and DUP was significant overall ($p=0.005$), although no individual variable reached statistical significance. In the full baseline cohort ($n=84$), negative-symptom predominance during the untreated psychosis period was associated with a markedly longer DUP than positive-symptom predominance (median, 104.0 vs. 12.5 weeks; $p<0.001$).

Conclusion: Symptomatic remission was common approximately four years after first admission, although individual baseline predictors showed limited independent explanatory power in this modestly sized cohort. Negative-symptom predominance during the untreated psychosis period was strongly associated with prolonged treatment delay, highlighting a potential target for earlier detection efforts.

Keywords: First-episode schizophrenia, remission, duration of untreated psychosis, negative symptoms, early intervention

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INTRODUCTION

Schizophrenia most commonly emerges in late adolescence or early adulthood, frequently becoming clinically apparent with a first psychotic episode. First-episode schizophrenia represents the subset of first-episode psychosis (FEP) in which the eventual diagnosis is established as schizophrenia (1). Despite its widespread use, however, FEP lacks a universally accepted operational definition. Three principal approaches have been used in the literature, defining the first episode according to first clinical contact, minimal or absent previous antipsychotic exposure, or the duration since the onset of psychotic symptoms (2). Among these, onset-based definitions may offer particular conceptual advantages by locating patients according to the course of illness rather than solely according to their first contact with services, which may occur substantially after symptom onset (2). Recent literature also suggests that onset-based definitions are among the most commonly adopted operational approaches (3). Conceptualizing the first episode in relation to illness onset is particularly relevant within the critical-period framework of schizophrenia, according to which a disproportionate degree of clinical and functional deterioration occurs during the early years of illness, making this period an important window for timely intervention and potentially influencing longer-term outcomes (4).

The FEP umbrella, however, encompasses a diagnostically heterogeneous group of conditions that differ substantially in etiology, diagnostic stability, clinical course, and long-term outcome (5). Although the underlying disorder can be identified reliably at first presentation in some patients, in others the diagnostic picture evolves over time and becomes apparent only through longitudinal observation. Individuals initially presenting with psychosis may ultimately receive diagnoses including brief psychotic disorder, substance-induced psychotic disorder, affective disorders with psychotic features, schizoaffective disorder, or schizophrenia. Large longitudinal studies have consistently demonstrated substantial diagnostic instability among acute and transient, affective, and substance-induced psychoses, whereas schizophrenia and schizophrenia-spectrum disorders show comparatively high prospective diagnostic stability (1, 6, 7). Because symptomatic course, functional trajectory, and long-term prognosis differ substantially across these diagnostic groups, longitudinal diagnostic refinement is essential when estimating outcomes specifically attributable to schizophrenia.

Symptomatic remission and recovery have consequently become central but distinct constructs for evaluating the course of schizophrenia. The Remission in Schizophrenia Working Group (RSWG) operationalized symptomatic remission as maintaining no more than mild severity across eight core positive, negative, and disorganization-related symptoms for at least six months (8). Importantly, symptomatic remission does not necessarily imply functional recovery; the RSWG conceptualized recovery as a more demanding outcome encompassing symptomatic improvement together with restoration of social and vocational functioning (8). Meta-analytic evidence in first-episode psychosis indicates that symptomatic remission is attainable in a substantial proportion of patients, although estimates decline with longer follow-up and vary considerably across studies (9). Recovery is less consistently achieved, particularly when definitions require improvement across both clinical and social or functional domains (9, 10). This distinction becomes even more apparent over longer periods: a meta-analysis of studies with at least 20 years of follow-up estimated recovery in approximately one-quarter of patients with schizophrenia (10), while the 20-year OPUS follow-up reported symptomatic remission in 40% and clinical recovery in 18% of assessed participants (11).

Despite substantial research, reliable prediction of remission and recovery after first-episode psychosis remains challenging. In a recent meta-analysis, none of the examined demographic, clinical, or study-level variables significantly moderated symptomatic remission, whereas only male sex and greater baseline positive symptom severity were associated with recovery estimates (3). These findings should be interpreted in light of the considerable methodological heterogeneity in the literature. First, many studies comprise diagnostically heterogeneous FEP cohorts, combining schizophrenia with affective, brief, and other psychotic disorders that may have substantially different trajectories and outcomes. Second, definitions of remission and, particularly, recovery vary considerably across studies, including differences in symptom thresholds, functional requirements, and duration criteria, which can produce markedly different outcome estimates (3, 12). Treatment-related heterogeneity, including antipsychotic exposure, adherence and discontinuation, and access to psychosocial or specialized early-intervention services, further complicates comparisons across cohorts (12). Follow-up duration and attrition represent additional

concerns, particularly in long-term studies, in which selective loss to follow-up may compromise the representativeness of the retained sample (13). Finally, repeated longitudinal assessments demonstrate that symptomatic and functional outcomes may change substantially over time, underscoring that remission or recovery observed at a single follow-up point does not necessarily represent a stable long-term outcome (14).

Beyond estimating remission and its associated factors, another clinically relevant question is whether the phenomenology of the untreated illness itself contributes to variation in DUP. Negative symptoms commonly develop insidiously and may be less behaviorally salient to patients, families, and clinicians than florid positive symptoms. Previous first-episode studies have linked avolition, anhedonia, social withdrawal, and related negative-symptom presentations to delayed help-seeking and longer pathways to treatment, whereas more acute or behaviorally conspicuous presentations may facilitate earlier recognition and contact with psychiatric services (15–18). A predominantly negative-symptom presentation may therefore contribute to a longer interval before treatment initiation. Examining this relationship in the entire baseline first-episode schizophrenia cohort, rather than only among participants retained at long-term follow-up, also allows this aspect of DUP to be investigated independently of subsequent follow-up attrition.

Given these limitations, further studies using diagnostically homogeneous samples and standardized outcome measures are needed to characterize the early course of schizophrenia and clarify how illness presentation during the untreated period may contribute to treatment delay. In Türkiye, schizophrenia-specific longitudinal outcome data remain limited, and much of the frequently cited first-episode evidence derives from cohorts established considerably earlier (19–24). The present study therefore examined a diagnostically homogeneous cohort restricted to patients whose diagnosis of schizophrenia was confirmed longitudinally and evaluated symptomatic remission using the RSWG framework. Specifically, we aimed to estimate the proportion of patients meeting symptomatic remission criteria approximately four years after first admission, explore baseline factors associated with remission, and examine whether positive- versus negative-symptom predominance during the untreated psychosis period was associated with DUP. By providing contemporary naturalistic data from a tertiary-care setting in Türkiye,

this study also seeks to update the limited regional evidence on early-course schizophrenia outcomes and inform further investigation of factors that may contribute to delayed recognition and treatment.

METHODS

Study Design, Setting, and Participants

This retrospective cohort study was conducted in the Department of Psychiatry of a tertiary-level hospital in Türkiye. The hospital provides psychiatric services to a defined catchment area and also receives referrals from other parts of the city because of its tertiary-care capacity. The source cohort was identified through a systematic search of the hospital's electronic medical records for all patients admitted to the adult inpatient psychiatry units with a first episode of psychosis between January 2020 and December 2022.

Eligibility criteria were: (i) presentation with an acute first psychotic episode; (ii) inpatient psychiatric treatment at the study hospital during the recruitment period; (iii) age between 15 and 50 years; and (iv) a diagnosis of schizophrenia established either during the index hospitalization or subsequently during longitudinal follow-up, as documented by the study institution or another psychiatric facility. For participation in the follow-up assessment, patients were additionally required to have sufficient attention and ability to cooperate with a face-to-face or telephone interview and to have a first-degree relative, preferably one living with or providing regular care for the patient, available for informant-based assessment of functioning.

A first psychotic episode was operationally defined by the absence of a previous diagnosis of an affective or non-affective psychotic disorder, previous exposure to antipsychotic medication, and previous psychiatric hospitalization. Patients were excluded if they were diagnosed at the index admission or during subsequent follow-up with organic psychosis, major depressive disorder with psychotic features, bipolar disorder with psychotic features, peripartum psychosis, or substance- or alcohol-induced psychosis. Current or previous alcohol or substance use disorder and medical or neurological conditions considered capable of contributing to psychotic symptoms or substantially confounding clinical outcomes were also exclusion criteria.

Application of these criteria yielded an initial cohort of 84 patients with a longitudinally confirmed diagnosis of schizophrenia. Although participants

had initially presented with first-episode psychosis, the final study cohort therefore comprised only those whose subsequent illness course supported a diagnosis of schizophrenia.

Data Collection and Follow-up Procedure

The study was conducted in two stages. In the first stage, demographic and clinical information relating to the index episode was extracted retrospectively from the electronic medical records of all 84 participants and recorded using standardized data collection forms developed by the research team. Variables included sex, age at illness onset, duration of first hospitalization, duration of untreated psychosis (DUP), number of psychiatric hospitalizations following the index admission, cumulative duration of subsequent hospitalizations, predominant symptom profile during the untreated psychosis period, marital status, educational level, employment status and living arrangement at illness onset, receipt of electroconvulsive therapy (ECT) during the index admission, smoking status at illness onset, and regular follow-up at the study institution after the first hospitalization.

The predominant symptom profile during untreated psychosis was classified as positive- or negative-symptom predominance based on clinical descriptions recorded for the untreated phase. DUP was defined as the interval, in weeks, between the onset of the first identifiable positive psychotic symptom and the index psychiatric hospitalization, which coincided with the first initiation of antipsychotic treatment. The onset of psychosis was determined using a best-estimate approach incorporating information from contemporaneous electronic medical records together with patient and family reports obtained during follow-up.

In the second stage, 39 of the original 84 participants (46.4%) were successfully contacted and reassessed. Loss to follow-up was primarily attributable to changed or discontinued registered telephone numbers and nonresponse despite repeated contact attempts. Four participants underwent face-to-face assessment, and 35 were assessed by telephone. Each interview lasted approximately 25–35 minutes. Written and/or verbal informed consent was obtained from participants and their relatives according to the mode of assessment.

At follow-up, current demographic, clinical, and functional characteristics were recorded using a second standardized data collection form. Variables included current marital status, educational level, employment status, living arrangement, medication

adherence, smoking status, lifetime history of suicide attempts, newly diagnosed general medical conditions, forensic events occurring during the illness course, symptomatic remission status, and current World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) total score.

Current medication adherence during the preceding month was assessed based on information obtained from both the patient and caregiver, supplemented by available medical records when accessible. Adherence was classified dichotomously as adherent or nonadherent on an overall clinical assessment of consistency with the prescribed medication regimen rather than a predefined quantitative threshold. No validated medication-adherence instrument was administered.

Assessment of Symptomatic Remission

Symptomatic remission at follow-up was assessed according to the severity component of the Remission in Schizophrenia Working Group (RSWG) criteria using the relevant items of the Positive and Negative Syndrome Scale (PANSS). The eight core items were delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), mannerisms/posturing (G5), unusual thought content (G9), blunted affect (N1), passive/apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6). A score of 3 or lower on each item was considered to satisfy the symptomatic severity criterion for remission. Only the PANSS items specified by the RSWG criteria were rated, rather than the complete 30-item scale. The PANSS and its Turkish adaptation have previously demonstrated established psychometric properties (25, 26).

Because symptom severity was assessed at a single follow-up time point and continuous item-level PANSS ratings covering the preceding six months were not available, the present analysis focused on cross-sectional symptomatic remission according to the RSWG severity criterion rather than independently verified sustained remission.

Functional Assessment

Functional disability was assessed using the 12-item proxy-reported World Health Organization Disability Assessment Schedule 2.0 (27, 28). The scale evaluates disability across six domains of functioning, with each item scored from 0 to 4 according to difficulties experienced during the preceding 30 days. A first-degree relative, preferably one living with or regularly caring for the participant, served as the informant. The scale was administered with interviewer assistance,

and only the total WHODAS 2.0 score was used in the analyses, with higher scores indicating greater functional disability.

WHODAS 2.0 was analyzed as a continuous measure of functional disability. No sample-derived WHODAS threshold was used to define functional recovery.

Statistical Analysis

Statistical analyses were performed using jamovi version 2.6.45.0. Continuous variables were examined for normality using the Shapiro–Wilk test together with inspection of skewness and kurtosis. Because the principal continuous variables did not meet the prespecified assumptions of normality, they were summarized using medians, interquartile ranges, and ranges. Categorical variables were summarized using frequencies and percentages.

For the total cohort of 84 patients, descriptive statistics were calculated for baseline demographic and clinical characteristics. Age at illness onset, duration of first hospitalization, and DUP were compared between patients with predominantly positive and predominantly negative symptoms during the untreated psychosis period using the Mann–Whitney U test. Rank-biserial correlation was reported as the effect-size measure for these comparisons.

Among the 39 participants who completed the follow-up assessment, exploratory bivariate comparisons were performed between participants who met and those who did not meet the symptomatic remission criterion. Continuous variables were compared using the Mann–Whitney U test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test when expected cell frequencies were small. Effect sizes were reported as rank-biserial correlations for continuous comparisons and Cramér's V for categorical comparisons, where appropriate. Variables measured concurrently at follow-up, including current WHODAS 2.0 score, medication adherence, current employment status, and current living arrangement, were interpreted as concurrent correlates of remission rather than temporally antecedent predictors.

An exploratory binomial logistic regression analysis was conducted to examine the independent associations of selected baseline variables with symptomatic remission. Remission was specified as the modeled outcome. To limit model complexity given the small follow-up sample, the model included three temporally antecedent variables: age at illness onset, sex, and DUP. Regression results were expressed

as regression coefficients, odds ratios, 95% confidence intervals, and p values.

Potential attrition-related differences were examined by comparing participants who completed the follow-up assessment (n=39) with those who did not (n=45) across baseline demographic and clinical characteristics available for the original cohort. Continuous variables were compared using the Mann–Whitney U test, whereas categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

All statistical tests were two-sided, and statistical significance was defined as $p < 0.05$.

Ethical Considerations

The study protocol (protocol no. 2025-288) was conducted in accordance with the Declaration of Helsinki and approved by the Cam ve Sakura City Hospital Clinical Research Ethics Committee on September 24, 2025. Written or verbal informed consent was obtained from all participants and their relatives in accordance with the mode of follow-up assessment.

RESULTS

A total of 84 patients with first-episode schizophrenia were included in the initial cohort. Of these, 59 (70.2%) were male and 25 (29.8%) were female. At illness onset, 18 patients (21.4%) were married and 22 (26.2%) were employed, while most participants were living with their parents and/or siblings (75.0%). Positive symptoms predominated during the untreated psychosis period in 64 patients (76.2%), whereas 20 (23.8%) had predominantly negative symptoms. Fifty-four patients (64.3%) maintained regular follow-up at our outpatient services after the index hospitalization. The median age was 27.0 years (interquartile range [IQR], 22.8–33.0), the median duration of untreated psychosis was 26.0 weeks (IQR, 4.0–52.0), and the median duration of the index hospitalization was 28.5 days (IQR, 21.0–38.0) (Table 1).

When the initial cohort was examined according to the predominant symptom profile during the untreated psychosis period, patients with predominantly negative symptoms had a markedly longer DUP than those with predominantly positive symptoms (median, 104.0 vs. 12.5 weeks; Mann–Whitney U=242, $p < 0.001$; rank-biserial correlation=0.623; median difference=–78.0 weeks, 95% confidence interval [CI], –103.0 to –44.0). In contrast, the groups did not differ significantly in age at illness onset (median, 24.0 vs.

Table 1: Baseline demographic and clinical characteristics of the first-episode schizophrenia cohort (n=84)

	n	%
Sex (n=84)		
Male	59	70.2
Female	25	29.8
Marital status at illness onset (n=84)		
Single	66	78.6
Married	18	21.4
Education level (n=73; data unavailable for 11 participants)		
No formal education	4	5.5
Primary school	13	17.8
Middle school	18	24.7
High school	23	31.5
University	15	20.5
Employment status at illness onset (n=84)		
Employed	22	26.2
Unemployed	62	73.8
Living arrangement at illness onset (n=84)		
With parents and/or siblings	63	75.0
With spouse	16	19.0
Alone	5	6.0
Symptom predominance during untreated psychosis (n=84)		
Positive-symptom predominance	64	76.2
Negative-symptom predominance	20	23.8
Regular outpatient follow-up after index hospitalization (n=84)		
Yes	54	64.3
No	30	35.7
Tobacco use at illness onset (n=84)		
Yes	43	51.2
No	41	48.8
ECT during index hospitalization (n=84)		
Yes	10	11.9
No	74	88.1
	Median (min–max)	IQR (Q1)IQR (Q3)
Age at illness onset (years) (n=84)	27.0 (18.0–48.0)	22.833.0
Duration of untreated psychosis (weeks) (n=84)	26.0 (1.0–312.0)	4.0052.0
Duration of index hospitalization (days) (n=84)	28.5 (4.0–87.0)	21.038.0

IQR: Interquartile range; ECT: Electroconvulsive therapy. Statistical significance was set at $p < 0.05$.

27.0 years; $p=0.383$) or duration of first hospitalization (22.5 vs. 29.0 days; $p=0.409$) (Table 2).

Follow-up assessment was completed in 39 of the 84 patients, of whom 28 met the cross-sectional symptomatic remission criterion and 11 did not, corresponding to a remission proportion of 71.8% (95% CI, 56.2%–83.5%). Remitters had an older median age at illness onset than non-remitters (28.5 vs. 23.0

years; $U=69.5$, $p=0.009$; median difference=6.0 years, 95% CI, 2.0–11.0; rank-biserial correlation=0.549). Functional disability differed substantially between the groups: the median current WHODAS 2.0 score was 3.5 among remitters compared with 26.5 among non-remitters ($p < 0.001$; median difference=-23.0, 95% CI, -26.0 to -16.0; rank-biserial correlation=-0.975). DUP was significantly shorter among remitters than

Table 2: Comparison of age at illness onset, duration of index hospitalization, and duration of untreated psychosis according to symptom predominance during untreated psychosis (n=84)

	n	Median	U	p	Rank-biserial r	Median difference	95% CI	
							Lower	Upper
Age at illness onset (years) (n=84)			557	0.383	-0.130	1.75	-2.00	5.00
Positive-symptom predominance	64	27.0						
Negative-symptom predominance	20	24.0						
Duration of index hospitalization (days) (n=84)			561	0.409	-0.123	3.00	-5.00	10.00
Positive-symptom predominance	64	29.0						
Negative-symptom predominance	20	22.5						
Duration of untreated psychosis (weeks) (n=84)			242	<0.001	0.623	-78.00	-103.00	-44.00
Positive-symptom predominance	64	12.5						
Negative-symptom predominance	20	104.0						

CI: Confidence interval. Statistical significance was set at $p < 0.05$.

among non-remitters (median, 16.5 vs. 52.0 weeks; $U=83.0$, $p=0.027$; rank-biserial correlation= -0.461). Duration of the index hospitalization, number of subsequent hospitalizations, and cumulative duration of subsequent hospitalizations did not differ significantly between groups (Table 3).

Several categorical characteristics showed nominal associations with remission status. Current living arrangements differed between groups (Fisher's exact $p=0.025$; Cramér's $V=0.414$); 32.1% of remitters were living with a spouse and/or children compared with none of the non-remitters. Current medication adherence showed the strongest categorical association with remission: 22 of 28 remitters (78.6%) were adherent compared with 2 of 11 non-remitters (18.2%; Fisher's exact $p < 0.001$; Cramér's $V=0.559$). No statistically significant differences were observed for sex, symptom predominance, marital status at illness onset, current marital status, educational level, employment status at illness onset, current employment, living arrangement at illness onset, ECT during the index admission, suicide attempts, smoking status, newly diagnosed general medical conditions, or forensic events (Table 3).

An exploratory binomial logistic regression model was subsequently fitted with remission as the modeled outcome and age at illness onset, sex, and DUP as baseline explanatory variables. The overall model was statistically significant ($\chi^2=13.0$, $df=3$, $p=0.005$; Nagelkerke $R^2=0.407$). However, none of the individual variables was independently statistically significant. Age at illness onset was associated with an odds ratio (OR) of 1.176 per year (95% CI, 0.982–1.41; $p=0.078$), female sex relative to male sex with an OR of 2.656 (95% CI, 0.342–20.63; $p=0.350$), and DUP with an

OR of 0.978 per additional week (95% CI, 0.956–1.00; $p=0.059$) (Table 4).

To examine potential attrition-related differences, baseline characteristics of the 39 participants who completed the follow-up assessment were compared with those of the 45 participants who did not. No statistically significant differences were identified between completers and non-completers in sex ($p=0.505$), age at illness onset ($p=0.914$), duration of first hospitalization ($p=0.812$), DUP ($p=0.746$), regular outpatient follow-up after the index hospitalization ($p=0.974$), predominant symptom profile ($p=0.240$), marital status at illness onset ($p=0.159$), educational level ($p=0.344$), employment status at illness onset ($p=0.696$), living arrangement at illness onset ($p=0.574$), receipt of ECT during the first hospitalization ($p=0.745$), or smoking status at illness onset ($p=0.194$) (Table 5).

DISCUSSION

In this retrospective cohort of patients with first-episode schizophrenia, we examined symptomatic remission approximately four years after first admission and explored baseline factors associated with remission, while also investigating the relationship between symptom predominance during the untreated psychosis period and DUP. Among participants who completed follow-up, symptomatic remission was observed in a substantial proportion, whereas negative-symptom predominance during the untreated phase was strongly associated with a markedly longer duration of untreated psychosis in the full baseline cohort. An important strength of the study is its use of a diagnostically homogeneous sample restricted to individuals with a longitudinally

Table 3: Comparison of participants meeting and not meeting the cross-sectional symptomatic remission criterion at follow-up (n=39)

	Remission group (n=28)	Non-remission group (n=11)	
Sex (male/female)	17/11	9/2	Fisher's exact p=0.276, Cramer's V=0.201
Age at illness onset – years (median)	28.5	23.0	U=69.5, p=0.009, MD=6.000, 95% CI=2.0-11.0, Rank-biserial r=0.5487
Duration of index hospitalization – days (median)	30.5	28.0	U=151.0, p=0.938, MD=1.000, 95% CI=-11.000-11.00, Rank-biserial r=0.0195
Duration of untreated psychosis – weeks (median)	16.5	52.0	U=83.0, p=0.027, MD=-23.329, 95% CI=-72.00-0.0000154, Rank-biserial r=-0.4610
Number of hospitalizations after index hospitalization (median)	0.0	0.0	U=125.5, p=0.600, MD=-0.0000596, 95% CI= -1.000-0.0000206, Rank-biserial r=0.1036
Total duration of hospitalizations after index hospitalization – weeks (median)	0.0	0.0	U=130.5, p=0.739, MD=-0.0000346, 95% CI= -3.000-0.000689, Rank-biserial r=0.0679
Current WHODAS 2.0 score (median)	3.50	26.5	U=3.50, p<0.001, MD=-23.000, 95% CI= -26.0-16.0, Rank-biserial r=-0.9750
Negative-symptom predominance during untreated psychosis, %	10.7% (3/28)	36.4% (4/11)	Fisher's exact p=0.083, Cramer's V=0.301
Married at illness onset, %	35.7% (10/28)	9.1% (1/11)	Fisher's exact p=0.130, Cramer's V=0.266
Currently married, %	25.0% (7/28)	9.1% (1/11)	Fisher's exact p=0.400, Cramer's V=0.177
Education level - % (n) (no formal education/primary school/middle school/high school/university)	7.1% (2/28)/21.4% (6/28)/21.4% (6/28)/28.6% (8/28)/21.4% (6/28)	0.0% (0/11)/36.4% (4/11)/9.1% (1/11)/36.4% (4/11)/18.2% (2/11)	Fisher's exact p=0.800, Cramer's V=0.245
Employed at illness onset - % (n)	25.0% (7/28)	36.4% (4/11)	Fisher's exact p=0.694, Cramer's V=0.114
Currently employed - %	32.1% (9/28)	9.1% (1/11)	Fisher's exact p=0.228, Cramer's V=0.238
Living arrangement at illness onset - % (n) (with parents/with spouse and/or children/alone)	64.3% (18/28)/28.6% (8/28)/7.1% (2/28)	81.8% (9/11)/9.1% (1/11)/9.1% (1/11)	Fisher's exact p=0.511, Cramer's V=0.208
Current living arrangement - % (n) (with parents/with spouse and/or children/alone)	67.9% (19/28)/32.1% (9/28)/0.0% (0/28)	90.9% (10/11)/0.0% (0/11)/9.1% (1/11)	Fisher's exact p=0.025, Cramer's V=0.414 (adjusted residual non-remission x with spouse and/or kids=-2.176)
Received ECT during index hospitalization - %	7.1% (2/28)	18.2% (2/11)	Fisher's exact p=0.562, Cramer's V=0.164
Currently adherent to medication - %	78.6% (22/28)	18.2% (2/11)	Fisher's exact p<0.001, Cramer's V=0.559
History of suicide attempt during the illness course - %	17.9% (5/28)	27.3% (3/11)	Fisher's exact p=0.663, Cramer's V=0.105
Tobacco use at illness onset - %	39.3% (11/28)	54.5% (6/11)	$\chi^2=0.748$, df=1, p=0.387, Cramer's V=0.138
Current tobacco use - %	50% (14/28)	63.6% (7/11)	Fisher's exact p=0.497, Cramer's V=0.123
Newly diagnosed general medical condition during the illness course - %	3.6% (1/28)	0.0% (0/11)	Fisher's exact p=1.000, Cramer's V=0.0982
New forensic event during the illness course - %	17.9% (5/28)	45.5% (5/11)	$\chi^2=3.15$, df=1, p=0.076, Cramer's V=0.284

Continuous variables are presented as medians. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using Pearson's χ^2 test or Fisher's exact test, as appropriate. Effect sizes are reported as rank-biserial correlations for continuous variables and Cramér's V for categorical variables. MD: Median difference; CI: Confidence interval; WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0; ECT: Electroconvulsive therapy. Statistical significance was set at p<0.05.

Table 4: Exploratory binomial logistic regression analysis of baseline factors associated with symptomatic remission

Predictor	Estimate	95% CI		SE	Z	p	OR	95% CI	
		Lower	Upper					Lower	Upper
Intercept	-2.6399	-7.3296	2.050	2.3927	-1.103	0.270	0.0714	0.00656	7.77
Age at illness onset (years)	0.1625	-0.0185	0.343	0.0923	1.759	0.078	1.1764	0.982	1.41
Sex: Female vs. male	0.9766	-1.0735	3.027	1.0460	0.934	0.350	2.6555	0.342	20.63
Duration of untreated psychosis (weeks)	-0.0221	-0.0451	0.00564	0.0117	-1.887	0.059	0.9781	0.956	1.00
Model fit				Overall model test					
Model	Deviance	AIC	R ² N	χ^2	df	p			
1	33.4	41.4	0.407	13.0	3	0.005			

Estimates represent the log odds of remission versus non-remission. The model was estimated using a sample of N=39. CI: Confidence interval; SE: Standard error; OR: Odds ratio; AIC: Akaike information criterion; df: Degrees of freedom; R²N: Nagelkerke's R². Statistical significance was set at p<0.05.

confirmed diagnosis of schizophrenia and examined within routine clinical practice at a tertiary psychiatric center in Türkiye.

The observed proportion of participants meeting the symptomatic remission criterion at follow-up was 71.8%, which is higher than the central estimates reported in earlier systematic reviews of first-episode schizophrenia (3, 9, 29). In the systematic review by AlAqeel and Margolese (29), remission rates ranged widely from 17% to 78%, but the median and weighted mean were only 40.0% and 35.6%, respectively, underscoring substantial heterogeneity across studies in follow-up duration, remission definitions, intervention exposure, and attrition. Our estimate should nevertheless be interpreted cautiously because only 39 of the original 84 participants were reassessed. Although no significant differences were detected in the measured baseline characteristics of completers and non-completers, selection based on unmeasured clinical characteristics remains possible and may have inflated the observed remission proportion. These observations also raise the question of whether differences in remission estimates across studies might partly reflect the era in which patients received treatment. However, relatively high remission proportions have been reported in both earlier and more contemporary cohorts. In the TIPS (Early Treatment and Intervention in Psychosis) cohort, recruited between 1997 and 2000, approximately 71% of participants were in symptomatic remission at two years (30), while Jaracz et al. (31), studying a schizophrenia cohort recruited between 1998 and 2002, demonstrated considerable longitudinal variability, with only 17.2% remaining in stable remission and 57.8% showing an unstable remission course over 7–11 years. More contemporary cohorts

have likewise reported relatively favorable short-term remission outcomes. For example, the Korean Early Psychosis Cohort, based on data collected between 2014 and 2018, reported symptomatic remission in 67.3% of participants at 12 months (32), while Kim et al. (33) reported a six-month remission rate of 77.7% in a first-episode schizophrenia cohort. These findings caution against equating publication date with treatment era and, more importantly, do not suggest a straightforward temporal relationship between advances in schizophrenia care and observed remission rates. This interpretation is also consistent with very-long-term meta-analytic evidence suggesting limited historical change in the overall prognosis of schizophrenia despite major developments in treatment (10). Thus, although improvements in contemporary schizophrenia care may have contributed to the relatively high remission proportion observed in our cohort, comparisons with earlier studies do not allow this effect to be disentangled from substantial methodological and clinical differences between cohorts, including diagnostic composition, follow-up duration, remission criteria, treatment setting, and attrition. Nevertheless, the present cohort provides an updated estimate from a Turkish tertiary-care setting, where the principal disease-specific first-episode schizophrenia outcome data available in the literature originate from cohorts established in the 1990s, such as the Üçok et al. (19, 21) follow-up project.

In exploratory bivariate analyses, later age at illness onset and shorter DUP were associated with symptomatic remission. Later age at onset has been associated with more favorable outcomes in some first-episode studies, although findings across cohorts have been inconsistent, and age at onset has not

Table 5: Comparison of baseline characteristics between follow-up completers and non-completers

	Completers (n=39)	Non-completers (n=45)	
Sex (male/female)	26/13	33/12	$\chi^2=0.444$, df=1, p=0.505
Age at illness onset – years (median)	26.0	27.0	U=865, p=0.914, MD=-0.000033, 95% CI=-3.00-3.00
Duration of index hospitalization – days (median)	30.0	27.0	U=851, p=0.812, MD=1.000, 95% CI=-6.00-7.00
Duration of untreated psychosis – weeks (median)	26.0	26.0	U=841, p=0.746, MD=-0.00005, 95% CI= -20.00-8.00
Regular outpatient follow-up after index hospitalization (yes)	64.1% (25/39)	64.4% (29/45)	$\chi^2=0.00106$, df=1, p=0.974
Negative-symptom predominance during untreated psychosis - %	17.9% (7/39)	28.9% (13/45)	$\chi^2=1.38$, df=1, p=0.240
Married at illness onset - %	28.2% (11/39)	15.6% (7/45)	$\chi^2=1.99$, df=1, p=0.159
Education level - % (n) (no formal education/primary school/middle school/high school/university) [completers n=39; non-completers n=34, data were unavailable for 11 non-completers]	5.1% (2/39) 25.6% (10/39) 17.9% (7/39) 30.8% (12/39) 20.5% (8/39)	5.9% (2/34) 8.8% (3/34) 32.4% (11/34) 32.4% (11/34) 20.6% (7/34)	Fisher's exact p=0.344
Employed at illness onset - % (n)	28.2% (11/39)	24.4% (11/45)	$\chi^2=0.153$, df=1, p=0.696
Living arrangement at illness onset - % (n) (with parents/with spouse and/or children/alone)	69.2% (27/39) 23.1% (9/39) 7.7% (3/39)	80% (36/45) 15.6% (7/45) 4.4% (2/45)	Fisher's exact p=0.574
Received ECT during index hospitalization - %	10.3% (4/39)	13.3% (6/45)	Fisher's exact p=0.745
Tobacco use at illness onset - %	43.6% (17/39)	57.8% (26/45)	$\chi^2=1.68$, df=1, p=0.194

Statistical significance was set at $p < 0.05$. ECT: Electroconvulsive therapy; CI: Confidence interval; df: Degrees of freedom.

emerged as a robust predictor of remission in meta-analytic evidence (34). Üçok et al. (21) previously identified age at onset or first admission among variables associated with remission in first-episode schizophrenia, whereas the more recent meta-analysis by Catalan et al. (3) found no significant overall effect of sociodemographic or clinical predictors on symptomatic remission. In the present cohort, DUP was also shorter among remitters in exploratory bivariate analysis, although the corresponding association did not reach statistical significance in the multivariable model. This finding should therefore be interpreted cautiously and as hypothesis-generating rather than as evidence of an independent prognostic effect. Current living arrangement and medication adherence were also associated with remission. The latter is consistent with previous longitudinal evidence, including the Turkish first-episode schizophrenia

cohort of Üçok et al. (21), in which medication adherence during the first six months of follow-up was higher among patients who subsequently achieved remission and remained independently associated with remission status in multivariable analysis. More broadly, antipsychotic discontinuation has been associated with increased relapse risk after first-episode psychosis, further supporting the clinical relevance of continued treatment engagement (12). However, adherence in the present study was assessed concurrently with remission rather than prospectively. Its temporal direction therefore cannot be established (35): sustained adherence may facilitate symptom control (36), whereas remission itself (37), or associated factors such as greater insight, treatment engagement, and medication tolerability (38), may in turn facilitate adherence. Current living arrangement and medication adherence should consequently be

regarded as correlates of remission status rather than antecedent predictors. In the multivariable analysis of our sample, restricted to age at onset, sex, and DUP, none of these variables independently predicted remission, despite the overall significance of the model. Given the small follow-up sample and only 11 non-remitters, the estimates were imprecise and should not be considered confirmatory. This uncertainty is consistent with the broader first-episode literature, in which individual prognostic factors have shown considerable heterogeneity (3).

Interestingly, symptom predominance during the untreated psychosis period was not associated with subsequent remission status in our sample, despite our expectation that negative-symptom predominance during the initial period of illness would be associated with a less favorable course. Previous longitudinal evidence has consistently implicated negative symptoms in poorer outcomes after first-episode psychosis. Gee et al. (39) identified distinct trajectories of negative symptoms during the first year of treatment and found that patients with elevated negative symptoms at baseline, whether these symptoms subsequently remained stable or decreased, were more likely to follow a persistently poor social-functioning trajectory. Similarly, in a seven-year follow-up of first-episode psychosis, Wunderink et al. (40) found that greater baseline negative-symptom severity independently predicted both relapse and poorer functional outcome, with baseline negative symptoms representing the strongest predictor of relapse in their model. Several considerations may account for the apparent discrepancy with our findings. First, our classification captured the relative predominance of positive versus negative symptoms only during the untreated phase rather than the severity or longitudinal persistence of negative symptoms. This distinction is important because negative symptoms may fluctuate substantially during the early course of psychosis. In the cohort of Gee et al. (39), only a small subgroup exhibited persistently high negative symptoms, whereas a substantial proportion of patients presenting with elevated negative symptoms showed improvement during the first year of treatment. Thus, an early negative-symptom-predominant presentation may not be equivalent to a persistent negative-symptom burden and may carry different prognostic implications (41, 42). Second, the substantial loss to follow-up in our cohort may have attenuated an underlying association, although baseline symptom predominance did not

differ significantly between completers and non-completers; therefore, selective attrition according to negative symptom predominance cannot be demonstrated from the present data. Nevertheless, differential disengagement remains plausible in long-term naturalistic follow-up. Of particular relevance, Wunderink et al. (40) reported that patients not included in their longitudinal cohort generally had poorer clinical and social profiles and that many had prematurely lost contact with mental health services, illustrating how long-term samples may preferentially retain patients with more favorable engagement and functioning. Prominent negative symptoms, particularly avolition and social withdrawal, may contribute to difficulties in sustained treatment engagement through their effects on motivation and social functioning (39, 40). Accordingly, the absence of an association between symptom predominance during untreated psychosis and remission in the present cohort should not be interpreted as evidence against the prognostic importance of negative symptoms. Rather, it may reflect the distinction between an early symptom-predominance phenotype and the severity and persistence of negative symptoms over time, compounded by the potential influence of selection and engagement processes inherent in long-term naturalistic follow-up. Lastly, family and caregiver attitudes, involvement, and willingness to facilitate continued treatment may independently influence service engagement; thus, even a patient with prominent negative symptoms may remain in regular care when relatives are actively involved in maintaining treatment contact. Conversely, limited caregiver involvement may increase the likelihood of disengagement irrespective of symptom profile.

A central finding of the present study, derived from the full baseline cohort ($n=84$) and therefore not subject to follow-up attrition, was that patients whose untreated psychosis phase was characterized by a predominance of negative rather than positive symptoms had a markedly longer duration of untreated psychosis (median, 104.0 vs. 12.5 weeks; $p<0.001$). This finding is clinically plausible because the phenomenology of emerging psychosis may itself influence the timing of help-seeking and treatment initiation. Negative symptoms such as avolition, social withdrawal, and loss of motivation may evolve insidiously and be less likely to prompt recognition by patients or their families, whereas disruptive and behaviorally salient psychotic symptoms may lead to earlier contact with psychiatric services. Indeed,

an earlier Turkish first-episode schizophrenia study by Üçok et al. (43) described DUP as the product of multiple patient-, family-, and illness-related factors, including withdrawal, social isolation, loss of motivation, and family responses to emerging illness. More recently, Drake et al. (15) explicitly proposed a “confounded presentation” mechanism, whereby severe excitement, hostility, and behavioral dysfunction may alarm patients and those around them and thereby accelerate presentation for treatment. Nevertheless, the direction of the association observed in our study cannot be established: negative-symptom predominance may prolong the pathway to care, prolonged untreated illness may alter the clinical presentation, or both may reflect an underlying insidious illness phenotype. This distinction is important when interpreting DUP as a prognostic factor. Longer DUP has repeatedly been associated with poorer symptomatic and functional outcomes after first-episode psychosis, but the mechanisms underlying this relationship remain debated (44, 45). In a previous diagnostically homogeneous Turkish first-episode schizophrenia cohort, Üçok et al. (43) found that shorter DUP was associated with greater improvement in overall and positive symptoms during the first hospitalization, although the magnitude of these associations was modest and improvement in negative symptoms was unrelated to DUP. In substantially larger first-episode cohorts, Drake et al. (15) subsequently demonstrated a curvilinear association between treatment delay and response across symptom dimensions, with longer DUP predicting poorer treatment response and the greatest apparent deterioration occurring early in the untreated period. However, observational associations between DUP and outcome do not necessarily establish that treatment delay itself is causal. Insidious onset and other unmeasured illness characteristics may contribute both to delayed presentation and to poorer subsequent outcomes, thereby confounding this relationship. Jonas et al. (45) further proposed a lead-time explanation, showing that patients with long and short DUP followed similar trajectories of psychosocial decline when illness course was aligned with psychosis onset rather than first hospitalization; they therefore suggested that DUP may partly index how far illness has progressed by the time of clinical detection rather than independently determining subsequent course. Importantly, however, lead-time bias does not fully account for the available evidence. In a prospective

first-episode psychosis incidence cohort followed sequentially for 20 years, O’Keeffe et al. (44) found that shorter DUP remained associated with more favorable trajectories across psychopathology, functioning, and quality of life, with effects persisting for up to two decades and not fully explained by premorbid characteristics or lead-time bias. Thus, rather than viewing DUP exclusively as either a causal treatment delay or an epiphenomenon of illness severity, the available evidence supports a more nuanced interpretation. DUP may simultaneously reflect a potentially reducible delay in access to effective treatment and characteristics of the underlying illness phenotype that influence recognition, help-seeking, and progression. Importantly, reducing this delay should not necessarily be equated with modification of the long-term illness trajectory. Although earlier treatment and specialized early-intervention services may improve outcomes during the early course of psychosis, long-term findings from trials such as OPUS (11) suggest that these initial advantages may diminish after specialized intervention is discontinued, cautioning against interpreting shorter DUP as evidence of durable modification of the underlying illness course.

Strengths and Limitations

Several strengths and limitations of the present study should be considered when interpreting the findings. A key strength is the use of a diagnostically homogeneous first-episode schizophrenia cohort treated under routine clinical conditions, allowing a naturalistic examination of symptomatic remission in real-world practice. The exclusion of comorbid substance use disorders and other psychotic disorders further enhanced sample specificity and reduced clinical heterogeneity, strengthening the study’s focus on schizophrenia-related illness trajectories.

However, several limitations warrant acknowledgment. First, the retrospective design precluded prospective assessment of the stability and duration of remission, limiting conclusions regarding its maintenance over time. Relatedly, sampling bias cannot be excluded, as patients who remained in contact with treatment services may represent those with more favorable outcomes. However, baseline comparisons between completers and non-completers revealed no statistically significant differences across the available demographic and clinical variables, providing some evidence against systematic attrition bias, although unmeasured differences cannot be excluded. Second, PANSS scores at discharge following

the first hospitalization were unavailable, preventing assessment of whether remission criteria were met at the end of the initial inpatient episode. Third, detailed data on antipsychotic type, dosage, and the use of long-acting injectable formulations or clozapine could not be reliably collected, largely because of recall difficulties among patients and caregivers, and therefore could not be examined as potential confounders. The lack of prospective, repeated symptom assessments also limited evaluation of early treatment response as a predictor of outcome. Additionally, the distribution of diagnostic subtypes within schizophrenia (e.g., disorganized, paranoid, and catatonic subtypes) and the exclusion of other psychotic disorders may have influenced the observed associations between duration of untreated psychosis and outcomes, potentially limiting generalizability. Fourth, most follow-up assessments were conducted by telephone. Although this approach facilitated reassessment of participants who might otherwise have remained unreachable, some PANSS items included in the RSWG severity criterion, particularly blunted affect and mannerisms/posturing, depend partly on direct behavioral observation and may therefore have been less reliably assessed than during face-to-face evaluation. The remission estimate should consequently be interpreted with this measurement limitation in mind. Fifth, inter-rater reliability was not formally assessed, and raters were not blinded to baseline records. Sixth, this was a single-center study, which may limit the generalizability of the findings to other clinical settings. Seventh, given the number of bivariate comparisons performed, no correction for multiple testing was applied; these findings should therefore be interpreted with this in mind. Eighth, the index admissions occurred between 2020 and 2022, overlapping substantially with the coronavirus disease 2019 (COVID-19) pandemic. Pandemic-related disruptions in healthcare access and help-seeking may have influenced DUP and hospitalization patterns and should be considered when comparing this cohort with earlier samples. Finally, remission was assessed at a single time point rather than as a dynamic trajectory. Given that achieving and maintaining remission are distinct processes, future studies should prioritize longitudinal, trajectory-based approaches and examine early clinical phenotypes, including paranoid and hebephrenic presentations, alongside factors such as insight, attitudes toward medication, and premorbid functioning, which may more accurately capture long-term outcome processes.

Ethical Approval: This study was approved by the Cam ve Sakura City Hospital Clinical Research Ethics Committee (Decision date: 24.09.2025 Number: 288).

Informed Consent: Written and verbal informed consent was obtained from participants and their relatives according to the mode of assessment.

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	Data acquisition	I.A.
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Category 2	Drafting manuscript	I.A.
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RESEARCH ARTICLE

The effect of acceptance and commitment therapy-based anger management training on psychological flexibility and aggression in bipolar disorder: A controlled pilot study

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ABSTRACT

Objective: This study aimed to examine preliminary changes in psychological inflexibility and self-reported aggression following Acceptance and Commitment Therapy (ACT)-based anger management training in patients with bipolar disorder hospitalized in a high-security forensic psychiatric hospital (HSFPH).

Method: This controlled pilot study included 20 patients diagnosed with bipolar disorder and hospitalized in an HSFPH, with 10 patients assigned to the experimental group and 10 to the control group. The experimental group participated in an eight-session, group-based anger management program incorporating ACT principles, including anger recognition, cognitive defusion, acceptance, values-based behavior, forgiveness, and assertive communication. The Buss-Perry Aggression Questionnaire (BPAQ) and Acceptance and Action Questionnaire-II (AAQ-II) were administered to both groups at baseline and after the intervention.

Results: The experimental group showed significant reductions in BPAQ scores and self-reported aggression following the intervention ($Z=-2.8$, $p<0.05$), whereas no significant changes were observed in the control group. Psychological inflexibility, as measured by the AAQ-II, also decreased significantly in the experimental group at posttest ($Z=-1.7$, $p<0.05$), whereas no significant change was detected in the control group.

Conclusion: These preliminary findings suggest that ACT-based anger management training may help reduce self-reported aggression and psychological inflexibility in patients with bipolar disorder treated in an HSFPH. Larger studies with longer follow-up periods are needed to determine the durability of these effects and their potential impact on clinically relevant outcomes, including rehospitalization.

Keywords: Acceptance and commitment therapy, aggression, anger, forensic psychiatry, group psychoeducation, psychological flexibility, psychological rigidity

INTRODUCTION

Anger is a multidimensional emotional state involving cognitive, physiological, and behavioral components

that emerges in response to perceived provocation or injustice (1). When difficulties in emotion regulation are present, anger is more likely to be expressed through maladaptive and potentially aggressive responses (2).

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Consistent with this view, anger has been identified as a central emotional process underlying aggressive behavior, particularly when regulatory capacities are impaired (2–4). Understanding the psychological processes that influence how individuals respond to anger may therefore be important for explaining why anger leads to maladaptive or aggressive responses in some individuals. From a process-based perspective, psychological flexibility provides a useful framework for understanding patterns of dysregulated anger and maladaptive responding. Psychological flexibility, the core construct of Acceptance and Commitment Therapy (ACT), refers to the capacity to remain in contact with the present moment and to persist in or modify behavior in accordance with personally valued goals despite the presence of difficult internal experiences. In contrast, within the ACT model, psychopathology is conceptualized in terms of psychological inflexibility, defined as a pattern of responding characterized by cognitive fusion, experiential avoidance, diminished contact with the present moment, self-as-content, a lack of values clarity, and uncommitted action (5, 6).

Within the psychological flexibility framework, anger-related difficulties may arise from processes such as cognitive fusion and experiential avoidance, which constrain adaptive responding, whereas greater psychological flexibility facilitates more effective emotion regulation and reduces the likelihood of maladaptive and aggressive behaviors (2, 6, 7). These processes may be particularly relevant to psychiatric conditions in which difficulties with anger and emotion regulation are frequently observed, including bipolar disorder. Anger is a common and clinically relevant feature of bipolar disorder and is not restricted to manic episodes; elevated anger has also been reported during bipolar depression, in bipolar II disorder, and outside acute manic states (8). Consistent with this, Johnson and Carver found that anger and aggression may persist even after remission in individuals with bipolar I disorder and that emotion-relevant impulsivity was associated with anger, hostility, verbal aggression, and physical aggression (9). Longitudinal evidence further supports the persistence of these difficulties, with Ballester et al. (10) reporting consistently higher levels of self-reported anger, hostility, and verbal and physical aggression in individuals with bipolar disorder than in psychiatric and healthy controls over a four-year follow-up period. The persistence of anger and aggression in bipolar disorder may be particularly relevant in forensic psychiatric settings, where

aggressive behavior has important clinical and safety implications. In this context, a recent study of male mentally disordered offenders hospitalized in a high-security forensic psychiatric unit in Türkiye identified bipolar disorder as one of the major diagnostic groups and examined factors associated with offense severity and repeated offending within this group (11). More broadly, in forensic psychiatric populations, anger represents a key proximal risk factor for aggression, with elevated anger levels and difficulties in emotion regulation associated with increased frequency and severity of aggressive behavior (12–14). Targeting anger may therefore be particularly relevant in forensic psychiatric settings, where the management of aggression is an important component of clinical care. This highlights the need for interventions that address anger-related processes and aggression among forensic psychiatric patients. Meta-analytic findings indicate that a range of psychosocial interventions effectively reduce anger, with cognitive behavioral therapies being the most extensively studied. Although relaxation-based approaches may show slightly larger effect sizes, overall differences between treatment modalities are modest, suggesting broadly comparable effectiveness across interventions (15, 16). In offender populations, cognitive behavioral anger management interventions have also been shown to reduce both aggression and recidivism, with reported reductions of approximately 23% in general reoffending and 28% in violent reoffending (17). These interventions are thought to exert their effects by targeting key mechanisms such as anger awareness, identification of triggers, cognitive restructuring of maladaptive appraisals, and development of adaptive coping and self-regulation skills, thereby enabling individuals to modulate emotional arousal and inhibit impulsive responses (18).

Acceptance and Commitment Therapy, a contextual behavioral approach within the broader cognitive behavioral tradition, directly targets psychological flexibility as its primary mechanism of change. A growing body of empirical evidence supports the effectiveness of ACT across a range of clinical conditions. Meta-analytic findings demonstrate that ACT yields moderate effects across randomized controlled trials, with treatment outcomes consistently associated with increases in psychological flexibility (19). This is further supported by mediation studies indicating that improvements in psychological flexibility account for reductions in psychological symptoms (20). Similarly, randomized controlled trials comparing ACT and

cognitive behavioral therapy for anxiety disorders have shown that ACT is equally effective, with treatment gains closely linked to improvements in psychological flexibility (21).

Accordingly, ACT-based interventions may be particularly relevant for addressing anger-related problems by targeting underlying processes such as cognitive fusion, experiential avoidance, and behavior disconnected from personal values. Consistent with this perspective, group-based ACT interventions have demonstrated improvements in anger-related processes, including reductions in anger rumination and impulsivity (22, 23).

Despite this growing body of research, studies examining ACT-based group interventions in forensic psychiatric hospital settings remain limited. In Türkiye, ACT-based group studies are scarce, and research involving individuals with severe mental disorders, such as bipolar disorder, and those with a history of criminal behavior is virtually nonexistent. Accordingly, the present controlled pilot study aimed to examine preliminary changes in psychological inflexibility and self-reported aggression following an eight-session ACT-based group intervention among patients receiving treatment in a forensic psychiatric hospital. It was hypothesized that participants receiving the ACT-based anger management intervention would show reductions in self-reported psychological inflexibility and aggression from baseline to post-intervention.

METHODS

Study Design

This controlled pilot study was conducted between December 2021 and March 2022 at a high-security forensic psychiatry hospital. The outcome measures were administered to the experimental and control groups before and after the intervention period. Ethical approval was obtained, and written informed consent was obtained from all participants. All procedures were conducted in accordance with the Declaration of Helsinki.

Participants

Participants were recruited from patients receiving inpatient treatment at a single-center high security forensic psychiatric hospital (HSFPH) in Türkiye. An a priori sample size calculation was not conducted. The sample comprised all eligible and consenting patients available at the study site during the recruitment period. Accordingly, the study was designed as an exploratory controlled pilot investigation intended

to provide preliminary outcome estimates rather than confirmatory evidence of intervention efficacy. The inclusion criteria were: (1) a diagnosis of bipolar disorder; (2) clinical remission, as determined by the treating psychiatrist through clinical evaluation and review of medical records; (3) no current manic, depressive, or psychotic episode; (4) expected hospitalization for the duration of the eight-week intervention, based on the clinical treatment plan and available judicial or discharge information; and (5) provision of informed consent. Patients with intellectual disability or clinical symptoms that could prevent meaningful participation in the group sessions were excluded.

During the study period, 58 patients were hospitalized in the forensic psychiatry unit. Of these, 28 patients diagnosed with bipolar disorder were assessed for eligibility. Six patients were excluded because of an active manic, depressive, or psychotic episode. The remaining 22 eligible patients provided informed consent and were enrolled in the study. All participants were male and diagnosed with bipolar disorder. Participants had been involved in various criminal offenses, including assault and property-related crimes, and had been referred to the forensic psychiatric hospital following judicial evaluation. All participants had undergone forensic psychiatric assessment and were considered to have diminished or no criminal responsibility due to their psychiatric condition. Their mean age was 36.2 years (standard deviation [SD]=8.5 years). All participants received routine pharmacological treatment; however, changes in medication type or dosage during the intervention were not systematically recorded.

Baseline Acceptance and Action Questionnaire-II (AAQ-II) and Buss-Perry Aggression Questionnaire (BPAQ) assessments were completed before group allocation. Participants were ranked according to their baseline BPAQ scores and assigned alternately to the experimental and control groups based on odd- and even-numbered ranks. No composite score combining the AAQ-II and BPAQ was calculated. Because a randomly generated allocation sequence was not used, the study was classified as a controlled pilot study. One participant in the experimental group was discharged by court order during the third week and could not complete the intervention, while one participant in the control group withdrew during the fifth week. Consequently, 20 participants completed the study and were included in the final analysis (experimental group, $n=10$; control group, $n=10$).

Table 1: Summary of the group therapy content

Sessions	Session content
Week 1	Baseline questionnaires; welcome and group guidelines; participant introductions; understanding and reframing anger; myths about anger; overview of ACT; introduction to mindfulness; exercise: focusing on the breath; homework: daily mindfulness practice
Week 2	Present-moment exercise: body scan; creative hopelessness; perceived benefits of anger; assessing the costs of anger; control as the problem; homework: diary of the costs of angry behavior
Week 3	Present-moment exercise: mindful observation of thoughts; how the mind creates anger; cognitive defusion as an alternative; strategies for defusing from thoughts; action as an alternative; homework: values writing and defusion practice
Week 4	Present-moment exercise: mindful eating as an acceptance exercise; mindful acceptance in daily living tasks: willingness practice
Week 5	Present-moment exercise: the sky and the weather; self-as-context values; peak moments exercise; values card sorting; homework: values clarification
Week 6	Present-moment exercise: the facts; forgiveness; assertive communication; homework: forgiveness practice
Week 7	Present-moment exercise: leaves on a stream; committed action; homework: committed-action practice
Week 8	Present-moment exercise: taking off the armor; barriers to committed action; final awareness exercise: the swamp and the lotus flower; post-intervention questionnaires

Procedures

The study was conducted in three consecutive phases. The Acceptance and Action Questionnaire-II and Buss–Perry Aggression Questionnaire were administered to participants in the experimental group before and after the group therapy sessions. Anger was operationalized as self-reported anger and assessed using the anger subscale of the BPAQ. The same measures were administered to the control group; however, the control group received no therapeutic intervention. No follow-up assessment was conducted because continuity of access to participants could not be ensured following discharge or changes in judicial status. Before administration of the measures, participants were informed about the purpose of the study and the structure of the sessions, and informed consent was obtained. The anger management program developed by Foret and Eaton (2014) was delivered once weekly, with each session lasting 90 minutes and including a 10-minute break. Patients participating in group therapy were brought to the meeting room from three different HSFPH units accompanied by a security guard. To encourage participation, food and beverages were provided during the break. After each session, patients returned to their units accompanied by a security guard. The sessions were conducted over eight weeks within the ACT framework. The intervention was delivered by the psychiatrist responsible for the forensic psychiatry unit, assisted by a clinical social worker with five years of forensic psychiatry experience. Both had completed foundational and supervised ACT training, attended all sessions,

and followed the structured protocol presented in Table 1. Due to the security and confidentiality procedures of the forensic psychiatry unit, sessions were not audio- or video-recorded. Although the structured protocol was followed, treatment fidelity was not evaluated by an independent assessor. The primary goal of the group therapy was to enhance patients' awareness of the dynamic interplay among their thoughts, emotions, and behaviors while fostering psychological flexibility. In this context, the intervention sought to equip patients with practical, skill-based strategies to modify maladaptive reactions and respond to internal experiences in a more adaptive and values-consistent manner.

In the first session, the nature and functions of anger were discussed. Patients were then asked to imagine a situation in which they had experienced anger, and the emotions, thoughts, physical sensations, impulses, and behaviors that emerged in that situation were identified and conceptualized as five components of anger. Myths about anger were also discussed interactively, and a present-moment awareness exercise was conducted. In the second session, the costs of attempting to suppress anger were discussed, and a creative hopelessness exercise was conducted. In the third and fourth sessions, patients were taught to defuse from anger-related thoughts and make room for emotions accompanying anger through acceptance-based exercises. In the fifth session, patients' values were explored using the tombstone exercise, and followed by an interactive discussion of how anger-related behaviors could move them away from their values. In the sixth session, forgiveness and

Table 2: Pretest and posttest scores in the experimental and control groups

	Experimental group (n=10)				Control group (n=10)			
	Pretest		Posttest		Pretest		Posttest	
	X	SD	X	SD	X	SD	X	SD
AAQ-II	41.40	5.60	21.20	8.70	37.20	7.70	37.60	7.23
BPAQ	109.80	18.43	81.20	18.70	107.10	10.00	104.50	14.40

SD: Standard deviation; AAQ-II: Acceptance and Action Questionnaire-II; BPAQ: Buss-Perry Aggression Questionnaire

assertive communication skills were addressed using the “pushing against the wall” exercise. In the seventh and eighth sessions, motivational work focused on identifying behaviors consistent with participants’ values and addressing underlying emotional wounds by “removing the anger armor.” A summary of the group therapy content is provided in Table 1.

Measures

The Acceptance and Action Questionnaire-II (24) is a seven-item self-report measure of psychological inflexibility. Each item is rated on a seven-point Likert-type scale, with higher scores indicating greater psychological inflexibility (i.e., lower psychological flexibility). The scale was adapted into Turkish in 2016 (25). In the present study, the internal consistency coefficient (Cronbach’s alpha) was 0.84 at pretest and 0.86 at posttest.

The Buss-Perry Aggression Questionnaire (26) is a 29-item self-report measure used to assess individual differences in aggression. The scale comprises four subscales: physical aggression, verbal aggression, anger, and hostility. Participants rate each item on a Likert-type scale, with higher scores indicating higher levels of aggression. A Turkish version of the scale has been adapted and validated (27), and previous studies have demonstrated its validity and reliability. In the present study, Cronbach’s alpha for the total scale was 0.85 at pretest and 0.87 at posttest. Given the small sample size of this pilot study, analyses focused on the total BPAQ score to limit the number of statistical comparisons, reduce the risk of Type I error, and avoid imprecise estimates associated with separate subscale analyses.

Data Analysis

IBM Statistical Package for the Social Sciences (SPSS) version 23 was used to conduct the statistical analyses. Each group consisted of 10 participants. Given the small sample size and non-normal distributions of the variables, nonparametric tests were used. Baseline equivalence between the experimental and control groups was examined using the Mann–Whitney U

test. Within-group changes from pretest to posttest were analyzed using the Wilcoxon signed-rank test. To directly assess whether the magnitude of change differed between groups, change scores (Δ =posttest – pretest) were calculated and compared using the Mann–Whitney U test. Effect sizes were calculated as r , with values of 0.10, 0.30, and 0.50 interpreted as small, medium, and large effects, respectively. Given the small sample size, reliable 95% confidence intervals for these nonparametric effect-size estimates could not be calculated.

RESULTS

Descriptive statistics for the pretest and posttest scores of the experimental and control groups are presented in Table 2. At baseline, the mean AAQ-II score was 41.40 (SD=5.60) in the experimental group and 37.20 (SD=7.70) in the control group. Following the intervention, the mean AAQ-II score in the experimental group decreased to 21.20 (SD=8.70), whereas that of the control group remained relatively stable (M =37.60, SD =7.23). Similarly, the mean BPAQ score in the experimental group decreased from 109.80 (SD=18.43) at pretest to 81.20 (SD=18.70) at posttest. In contrast, the control group showed only a slight decrease in BPAQ scores, from 107.10 (SD=10.00) to 104.50 (SD=14.40). Changes in the mean AAQ-II and BPAQ scores of the experimental and control groups from pretest to posttest are illustrated in Figure 1. Error bars represent ± 1 standard deviation.

To determine whether the experimental and control groups differed at baseline, Mann–Whitney U tests were conducted on the pretest scores (Table 3). There were no statistically significant differences between the experimental and control groups in psychological inflexibility (AAQ-II; U =31.00, Z =–1.40, p =0.165) or aggression (BPAQ; U =38.50, Z =–0.87, p =0.393) at pretest. Thus, no statistically significant baseline differences were detected between the groups.

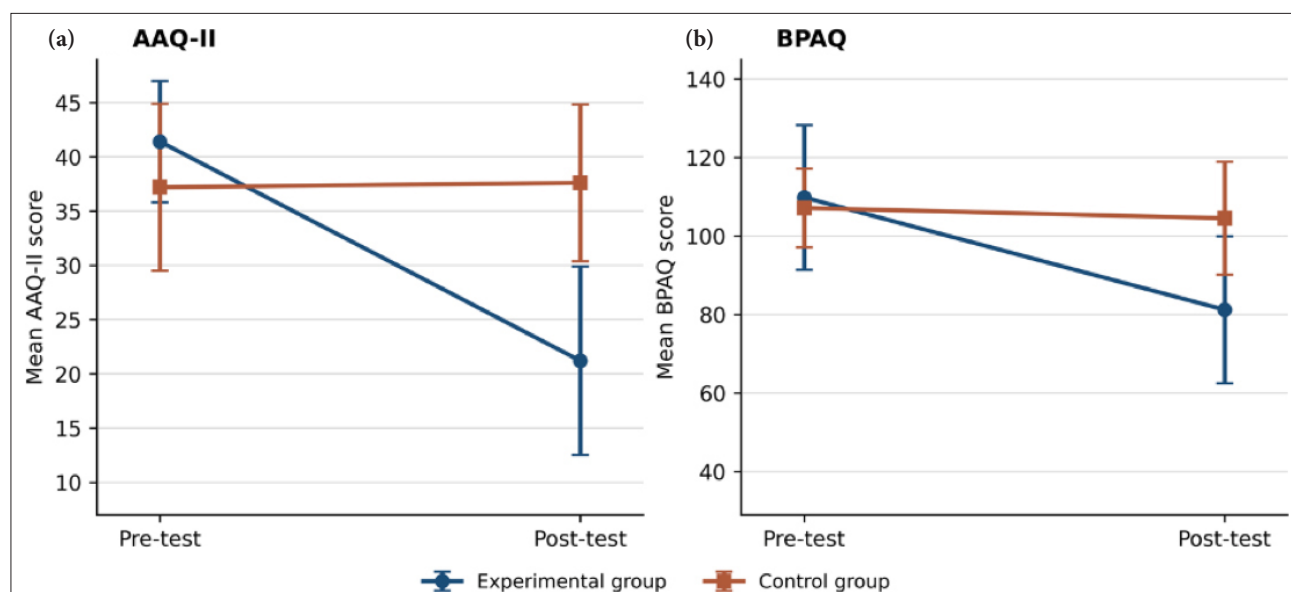


Figure 1. Changes in mean AAQ-II and BPAQ scores from pre-test to post-test in the experimental and control groups. Note. Error bars represent ± 1 standard deviation.

Table 3: Baseline comparisons between the experimental and control groups using the Mann–Whitney U test

Variables	Group	Mean rank	U	Z	p	Effect size (r)
AAQ-II	Experimental	12.40	31.00	-1.40	0.165	0.31
	Control	8.60				
BPAQ	Experimental	11.65	38.50	-0.87	0.393	0.19
	Control	9.35				

AAQ-II: Acceptance and Action Questionnaire-II; BPAQ: Buss-Perry Aggression Questionnaire. Note: Experimental group, n=10; control group, n=10.

Table 4: Within-group comparisons of pretest and posttest scores using the Wilcoxon signed-rank test

Variables	Group	Negative ranks	Positive ranks	Ties	Z	p	Effect size (r)
AAQ-II	Experimental	9	1	0	-1.70	0.044	0.54
	Control	5	4	1	-0.85	0.750	0.27
BPAQ	Experimental	10	0	0	-2.80	0.003	0.89
	Control	4	2	4	-0.53	0.590	0.17

AAQ-II: Acceptance and Action Questionnaire-II; BPAQ: Buss-Perry Aggression Questionnaire. Note: Experimental group, n=10; control group, n=10.

Within-group changes from pretest to posttest were examined using the Wilcoxon signed-rank test (Table 4). In the experimental group, a statistically significant difference was found between pretest and posttest AAQ-II scores ($Z=-1.70$, $p=0.044$), with a large effect size ($r=0.54$). Examination of the rank distributions showed that most participants in the experimental group had lower posttest than pretest scores. Lower posttest AAQ-II scores indicate lower levels of self-reported psychological inflexibility. In contrast, no statistically significant change was observed in the control group ($Z=-0.85$, $p=0.750$). For aggression measured by the BPAQ, a

statistically significant reduction was observed in the experimental group from pretest to posttest ($Z=-2.80$, $p=0.003$), with a large effect size ($r=0.89$). The rank distribution indicated that posttest aggression scores were lower than pretest scores for all participants in the experimental group. No statistically significant change was observed in the control group ($Z=-0.53$, $p=0.590$, $r=0.17$). The effect sizes observed in the control group were small for both outcomes.

Direct between-group comparisons of change scores indicated that the reduction in AAQ-II scores was significantly greater in the experimental group ($M\Delta=-20.20$, mean rank=6.00) than in the control

Table 5: Between-group comparisons of change scores (Δ ="Posttest"- "Pretest") using the Mann–Whitney U test

Variables	Group	Mean change (Δ)	Mean rank	U	Z	p	Effect size (r)
AAQ-II	Experimental	-20.20	6.00	5.00	-3.40	0.001	0.76
	Control	+0.40	15.00				
BPAQ	Experimental	-28.60	6.60	11.00	-2.95	0.003	0.66
	Control	-2.60	14.40				

AAQ-II: Acceptance and Action Questionnaire-II; BPAQ: Buss-Perry Aggression Questionnaire.

group ($M\Delta=+0.40$, mean rank=15.00; $U=5.00$, $Z=-3.40$, $p=0.001$, $r=0.76$). Similarly, the reduction in BPAQ scores was significantly greater in the experimental group ($M\Delta=-28.60$, mean rank=6.60) than in the control group ($M\Delta=-2.60$, mean rank=14.40; $U=11.00$, $Z=-2.95$, $p=0.003$, $r=0.66$). Both between-group comparisons yielded large effect sizes, reflecting greater reductions in psychological inflexibility and self-reported aggression in the experimental group (Table 5).

DISCUSSION

The present controlled pilot study examined preliminary changes in aggression and psychological inflexibility following ACT-based anger management training among patients in a forensic psychiatric hospital. No statistically significant baseline differences were detected between the experimental and control groups in AAQ-II or BPAQ scores. Direct between-group comparisons of change scores indicated greater reductions in both psychological inflexibility and self-reported aggression in the experimental group, with large effect sizes. These findings provide preliminary support for the potential usefulness of ACT-based anger management training in forensic psychiatric settings. However, given the small sample size and systematic rather than random allocation, the findings should be interpreted as preliminary evidence of differential change rather than definitive evidence of intervention efficacy.

Psychological inflexibility refers to rigid responses to internal experiences that interfere with values-based actions (28). Previous studies have demonstrated associations between psychological inflexibility and psychopathology, as well as between psychological flexibility and positive treatment outcomes (29–32). Improvements in psychological flexibility following ACT group therapy have also been reported among patients diagnosed with bipolar disorder (33, 34). Polat and Asi Karakaş reported that ACT-based anger management training significantly reduced anger rumination

and impulsivity in forensic psychiatric patients (22). Consistent with these findings, the present study observed preliminary reductions in self-reported aggression and psychological inflexibility following ACT-based anger management training. However, the present study differs from previous research in its assessment of psychological inflexibility using the AAQ-II. Whereas anger rumination reflects repetitive thinking about anger-provoking experiences and is associated with difficulties in anger regulation and maladaptive behavior, psychological inflexibility represents a construct more directly related to the theoretical framework of ACT. Therefore, assessing psychological inflexibility in the present study extends previous research by examining an ACT-related process alongside changes in aggression. The ACT-based anger management training program aimed to enhance psychological flexibility among HSFPH patients through interventions targeting cognitive defusion, acceptance of emotions, self-as-context, values, committed action, and present-moment awareness. During the ACT-based group therapy sessions, patients were encouraged to observe anger-related thoughts without attempting to suppress them, increase awareness of bodily sensations associated with anger without engaging in impulsive reactions, and develop acceptance of anger rather than attempting to avoid or eliminate it.

Clinical observations suggested that anger may, in some cases, function as a secondary response to the suppression of more distressing emotions, such as guilt, inadequacy, or worthlessness (35, 36). This interpretation is consistent with emerging literature in forensic and contextual behavioral science highlighting the roles of emotional suppression, experiential avoidance, and psychological inflexibility in anger and reactive aggression (7, 36, 37). From an ACT perspective, increased willingness to experience emotions preceding anger may represent one possible explanation for the observed changes; however, these specific processes were not directly assessed in the present study. In our study, a significant difference was observed between the

pretest and posttest AAQ-II scores of participants in the experimental group. Given that the AAQ-II assesses experiential avoidance and psychological inflexibility, the lower posttest AAQ-II scores observed in the experimental group are consistent with reduced psychological inflexibility following the intervention. No significant difference was observed between the pretest and posttest AAQ-II scores in the control group. These preliminary findings suggest that the ACT-based anger management training program may be associated with reduced psychological inflexibility among participants in the experimental group.

Future studies with longer-term follow-up are needed to determine whether reductions in psychological inflexibility are maintained after discharge and whether they are associated with broader clinical outcomes, including emotion regulation, interpersonal functioning, and aggressive behavior. Taken together, these findings provide preliminary support for the potential feasibility and usefulness of ACT-based anger management training among patients in HSFPHs. To our knowledge, this is among the first studies to examine changes in psychological flexibility following ACT-based group therapy in a high-security forensic psychiatric hospital setting. However, given the pilot nature of the study, small sample size, systematic allocation procedure, and absence of follow-up assessments, these findings should be interpreted cautiously and require confirmation in larger, adequately powered randomized controlled trials. The findings highlight the potential value of further investigating psychological flexibility and anger management interventions as adjuncts to pharmacological treatment in forensic psychiatric care.

Strengths and Limitations

Several limitations should be considered when interpreting the findings. First, the small, single-center, all-male sample and systematic rather than random allocation limit the generalizability and causal interpretation of the results. Although change-score comparisons directly assessed whether the magnitude of change differed between groups, this approach did not constitute an integrated group-by-time model or adjust for baseline variation. Therefore, the findings should be interpreted as preliminary rather than definitive evidence of intervention efficacy. Second, long-term follow-up assessments could not be conducted because access to participants could not be maintained after

discharge. Although all participants received routine pharmacological treatment, changes in medication type or dosage during the intervention were not systematically recorded, and detailed forensic and clinical characteristics could not be reported because of institutional and ethical restrictions. Participants also could not be assessed under real-life provocative conditions during hospitalization. In addition, the use of self-report measures may have introduced response-related biases, including difficulties in understanding questionnaire items or inaccuracies in self-reporting. Furthermore, because some assessments were administered by therapists involved in delivering the intervention, the possibility of assessor-related bias cannot be excluded.

Despite these limitations, the findings provide preliminary evidence regarding the potential usefulness of ACT-based interventions in forensic psychiatric settings. A major strength of the study is its focus on a forensic psychiatric population that remains underrepresented in psychotherapy research.

CONCLUSION

This controlled pilot study provides preliminary evidence regarding the potential usefulness of ACT-based anger management training for reducing self-reported aggression and psychological inflexibility among patients treated in HSFPH settings. Broader implementation of ACT-based interventions may contribute to improvements in psychological flexibility and emotional regulation, which could potentially support patients' quality of life and interpersonal functioning. In addition, increasing ACT training opportunities for experienced mental health professionals working in HSFPH settings may facilitate the development of group-based interventions. Future studies with larger samples and more comprehensive assessment methods may help further clarify the effectiveness of ACT-based group therapy interventions in forensic psychiatric hospitals.

Ethical Approval: This study was approved by the Ethics Committee of Kayseri City Hospital, (Decision no. 56, Dated 11.11.2021).

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Contribution Categories		Author Initials
Category 1	Concept/Design	T.K., H.K.
	Data acquisition	T.K., H.K.
	Data analysis/Interpretation	T.K., H.K.
	Case Follow-up (if applicable)	T.K., H.K.
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RESEARCH ARTICLE

Personal and social functioning, formal thought disorder, and executive functioning in violent offenders with schizophrenia: A cross-sectional study

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ABSTRACT

Objective: Functional impairment is a major determinant of long-term outcomes in schizophrenia and is influenced by multiple clinical and cognitive factors. Although formal thought disorder (FTD) has been associated with adverse outcomes, its relationship with functioning in patients with schizophrenia and a history of violent offending remains unclear. This study investigated the relationships among FTD, executive functioning, and personal and social functioning in this population.

Method: This cross-sectional study included 64 inpatients with schizophrenia and a history of violent offending. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS), depressive symptoms using the Calgary Depression Scale for Schizophrenia (CDSS), formal thought disorder using the Thought and Language Disorder Scale (TALD), executive functioning using the Frontal Assessment Battery (FAB), and personal and social functioning using the Personal and Social Performance Scale (PSP). Spearman correlation and multiple linear regression analyses were performed to identify factors associated with functioning.

Results: Poorer functioning was associated with greater psychopathology and more severe FTD. Subjective negative thought disorder showed the strongest associations with poorer functioning, including socially useful activities, interpersonal relationships, and self-care (all $p < 0.01$). Executive functioning, particularly verbal fluency, was positively associated with functioning; however, subjective negative thought disorder remained the only independent predictor of PSP total scores ($\beta = -0.324$, $p = 0.032$).

Conclusion: Formal thought disorder, particularly its subjective negative dimension, appears to be an important determinant of personal and social functioning in patients with schizophrenia and a history of violent offending. These findings highlight the importance of assessing thought disorder beyond overall symptom severity and suggest that interventions targeting communication and thought organization may support functional recovery in forensic schizophrenia populations.

Keywords: Schizophrenia, executive function, social adjustment, violence, aggression

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INTRODUCTION

Schizophrenia is a chronic and clinically heterogeneous psychiatric disorder characterized by disturbances in perception, thought processes, affect regulation, and behavior. In addition to positive symptoms such as delusions and hallucinations, individuals frequently experience negative symptoms and persistent cognitive impairments that significantly affect social, occupational, and interpersonal functioning throughout the course of illness (1, 2). Functional impairment is increasingly recognized as one of the most important determinants of long-term outcomes in schizophrenia and is conceptualized as a multidimensional construct shaped not only by psychotic symptoms but also by deficits in cognition, motivation, communication, and social adaptation (3). Despite advances in pharmacological treatment, functional recovery remains limited for many patients, highlighting the need to identify clinical and cognitive factors associated with real-world functioning.

Although most individuals with schizophrenia are not violent, epidemiological studies have consistently reported a modest but reliable increase in the risk of violent behavior compared with the general population (4, 5). Violent offending in schizophrenia is thought to arise from the interaction of multiple vulnerability factors, including substance use, treatment nonadherence, previous violence, social disadvantage, and symptom-related factors (6–8). Patients with a history of violent offending may experience greater clinical complexity and poorer psychosocial outcomes, making this subgroup particularly relevant for studies investigating factors associated with functional outcomes.

Cognitive dysfunction is increasingly regarded as a core feature of schizophrenia and a major contributor to poor functional outcome. Deficits in executive functioning, cognitive flexibility, working memory, inhibitory control, and social cognition often persist beyond acute psychotic episodes and are closely associated with impaired community functioning (1, 9). Executive dysfunction may compromise an individual's ability to regulate behavior, accurately interpret environmental cues, solve interpersonal problems, and engage effectively in daily activities. Previous studies have reported mixed findings regarding executive functioning in patients with schizophrenia and a history of violent offending. While some studies have identified greater executive dysfunction and poorer decision-making

abilities in violent offenders, others have found no significant differences or even better performance in specific cognitive domains. Nevertheless, executive functioning remains an important construct to investigate because impairments in executive processes may contribute to behavioral regulation, social adaptation, and functional outcomes in schizophrenia (5, 10–14).

Formal thought disorder (FTD) is another central feature of schizophrenia and refers to disturbances in the organization, structure, and expression of thought. Clinically, FTD may manifest as derailment, tangentiality, incoherence, perseveration, poverty of speech, or subjective experiences of thought interference and fragmentation (15). Contemporary dimensional models distinguish between objective and subjective manifestations of thought disorder, as well as positive and negative dimensions, which may reflect partially distinct neurocognitive mechanisms (16). Beyond its diagnostic significance, FTD has been associated with impaired communication, reduced social competence, poorer functional outcomes, and deficits in executive control and semantic processing (17). Although recent studies have highlighted the contribution of specific dimensions of FTD to violent offending in schizophrenia (18), considerably less is known about how these dimensions relate to personal and social functioning in patients with schizophrenia and a history of violent offending. Consequently, it remains unclear whether thought disorder is associated with functional impairment independently of symptom severity and executive dysfunction.

Emerging evidence suggests that disturbances in thought organization may be particularly relevant in forensic schizophrenia populations. Difficulties in maintaining coherent thought processes and accurately interpreting interpersonal situations may contribute not only to maladaptive behavioral responses but also to reduced social and occupational functioning (19, 20). Nevertheless, the relationships among FTD, executive functioning, and functional outcomes remain insufficiently explored. Existing studies are limited by methodological heterogeneity, small forensic samples, and a tendency to examine cognition and thought disorder separately rather than within an integrated framework. Furthermore, few studies have simultaneously investigated executive functioning, FTD, and personal and social functioning within the same sample of patients with schizophrenia and a history of violent offending. A better understanding of these relationships may

inform individualized rehabilitation strategies and improve the assessment of factors associated with functional recovery in forensic psychiatric settings.

Accordingly, the present study aimed to investigate the relationships among FTD, executive functioning, and personal and social functioning in patients with schizophrenia and a history of violent offending and to identify factors independently associated with functional outcomes within this forensic sample. We hypothesized that greater FTD severity and poorer executive functioning would be associated with lower levels of personal and social functioning.

METHODS

Participants

This cross-sectional study included 64 inpatients diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. All participants were recruited from the High-Security Forensic Psychiatry Unit of Ankara Bilkent City Hospital between August 2024 and January 2025. The sample consisted exclusively of patients with a documented history of violent offending.

No a priori power analysis was performed because the study included a consecutive sample of all eligible patients admitted to the High-Security Forensic Psychiatry Unit during the predefined study period. Therefore, the sample size was determined by the number of patients meeting the inclusion criteria rather than by a predefined statistical calculation.

Violent offending was defined as a legally documented act involving physical harm or the threat of physical harm to another person or property, confirmed through judicial records and forensic clinical files. Eligible participants were 18–55 years of age, had sufficient literacy and cognitive capacity to complete the clinical interviews and psychometric assessments, demonstrated adequate cooperation throughout the assessment process, and provided written informed consent before participation. Exclusion criteria included intellectual disability, dementia or other neurological disorders, acute substance intoxication at the time of assessment, illiteracy, and receipt of electroconvulsive therapy during the study period. Acute substance intoxication was excluded based on clinical evaluation and negative urine toxicology screening performed at hospital admission. Clinically evident intellectual disability was excluded based on clinical evaluation and review of medical records rather than standardized psychometric testing.

All evaluations were conducted face-to-face by clinicians experienced in forensic psychiatry while participants were in a clinically stable phase, defined as the absence of acute psychotic exacerbation requiring immediate treatment modification and the presence of adequate cooperation during clinical interviews and psychometric assessments.

Clinical and Cognitive Assessment

Sociodemographic and clinical characteristics, including illness duration, treatment history, substance use, and forensic history, were obtained from medical records and structured clinical interviews using a standardized data collection form.

Psychotic symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) (21), which evaluates positive symptoms (seven items), negative symptoms (seven items), and general psychopathology (16 items). The PANSS comprises 30 items rated from 1 to 7, with total scores ranging from 30 to 210; higher scores indicate greater symptom severity. The Turkish validity and reliability study was conducted by Kostakoğlu et al. (22).

Depressive symptoms were evaluated using the Calgary Depression Scale for Schizophrenia (CDSS), a clinician-rated instrument specifically developed to assess depressive symptoms in schizophrenia while minimizing overlap with negative and extrapyramidal symptoms (23). The CDSS comprises nine items scored from 0 to 3, with total scores ranging from 0 to 27; higher scores indicate greater depressive symptom severity. The Turkish validity and reliability study was conducted by Aydemir et al. (24).

Personal and social functioning was assessed using the Personal and Social Performance Scale (PSP), which provides a total score ranging from 1 to 100 and evaluates functioning across four domains: socially useful activities, personal and social relationships, self-care, and disturbing or aggressive behaviors. Higher total scores indicate better overall functioning (25, 26).

Formal thought disorder was evaluated using the Thought and Language Disorder Scale (TALD), a 30-item, semistructured, clinician-rated instrument in which each item is scored from 0 (absent) to 4 (severe), yielding a total score ranging from 0 to 120. The TALD assesses four dimensions of formal thought disorder: objective positive, objective negative, subjective positive, and subjective negative. Objective dimensions are based on the clinician's observations of speech and language abnormalities, whereas subjective dimensions reflect the patient's self-

reported experiences of disturbed thinking. Positive dimensions reflect disorganization and productive thought abnormalities, whereas negative dimensions reflect impoverishment and reduction of thought and language (27). The Turkish validity and reliability study was conducted by Mutlu et al. (28).

Executive functioning was assessed using the Frontal Assessment Battery (FAB) (29), which comprises six subtests assessing conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. Total FAB scores range from 0 to 18, with higher scores indicating better executive functioning. The Turkish validity and reliability study was conducted by Tunçay (30).

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Ankara Bilkent City Hospital (August 7, 2024; approval number: 1-24-470).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ standard deviation (SD), whereas categorical variables are presented as frequencies and percentages. Sex-stratified comparisons of continuous variables were performed using independent-samples *t* tests.

Normality assumptions were evaluated using the Shapiro–Wilk test together with skewness and kurtosis values. Because several clinical variables showed non-normal distributions, associations between functioning measures and clinical variables were examined using Spearman rank correlation coefficients.

Correlation analyses were performed to investigate the relationships between PSP total and subscale scores and measures of psychopathology (PANSS and CDSS), formal thought disorder (TALD), and executive functioning (FAB).

To identify factors independently associated with personal and social functioning, a multiple linear regression analysis was conducted with the PSP total score as the dependent variable. Variables were selected for inclusion in the regression model based on their bivariate associations with PSP total scores and clinical relevance. Among the TALD dimensions, subjective negative thought disorder was selected because it showed the strongest association with overall functioning. To minimize multicollinearity, PANSS positive and general psychopathology scores were excluded because of high variance inflation factor (VIF) values; PANSS negative symptoms were

Table 1: Sociodemographic and clinical characteristics of the participants

	Patients (n=64)
Age (years)	40.39 $\pm$ 10.07
Male sex, n (%)	47 (73.4)
Education (years)	10.31 $\pm$ 4.08
Smoking duration (years)	13.20 $\pm$ 11.97
Alcohol use duration (years)	0.75 $\pm$ 3.75
Substance use duration (years)	0.23 $\pm$ 1.88
Age at symptom onset (years)	24.66 $\pm$ 8.67
Age at first psychiatric admission (years)	26.19 $\pm$ 8.55
Duration of illness (years)	14.3 $\pm$ 9.2
Duration of antipsychotic treatment (years)	7.42 $\pm$ 6.20
Duration of untreated psychosis (years)	6.91 $\pm$ 8.80
Number of hospitalizations	2.36 $\pm$ 2.06
Antipsychotic dose (chlorpromazine equivalent, mg)	602.28 $\pm$ 375.43
Antipsychotic dose (risperidone equivalent, mg)	9.03 $\pm$ 5.64
Body mass index (BMI)	27.68 $\pm$ 5.64

Values are presented as mean $\pm$ standard deviation unless otherwise indicated.
BMI: Body mass index.

therefore included as the psychopathology measure. The FAB total score was included as the measure of executive functioning. Standardized beta coefficients (β), model fit statistics, and explained variance (R^2) were reported. Statistical significance was set at $p < 0.05$ (two-tailed).

RESULTS

The sociodemographic and clinical characteristics of the study sample are presented in Table 1. The sample consisted predominantly of male patients (73.4%), with a mean age of 40.39 $\pm$ 10.07 years. The mean duration of illness was 14.3 $\pm$ 9.2 years, and the mean duration of untreated psychosis was 6.91 $\pm$ 8.80 years. Participants had received antipsychotic treatment for a mean duration of 7.42 $\pm$ 6.20 years. Regarding the characteristics of violent offending, 82% of patients had a history of person-directed violence, whereas 18% had committed property-related offenses. Sex-stratified analyses showed no significant differences between male and female participants in psychopathology, FTD, executive functioning, or personal and social functioning. Female participants were older than male participants (Appendix1).

Table 2: Psychopathology, thought and language disorder, functioning, and executive function scores

Measure	Mean±SD
PANSS	
Total score	71.53±16.50
Positive symptoms	16.05±5.56
Negative symptoms	18.34±6.13
General psychopathology	37.41±9.13
TALD	
Objective positive	12.05±5.59
Subjective negative	6.47±3.12
Objective negative	6.30±4.29
Subjective positive	1.64±1.12
FAB	
Total score	13.38±3.50
Conceptualization	2.31±0.88
Verbal fluency	1.67±0.92
Programming	2.31±0.97
Sensitivity to interference	2.30±0.93
Inhibitory control	2.16±0.97
Environmental autonomy	2.64±0.74
PSP	
Total score	61.64±13.09
Socially useful activities	14.22±4.73
Personal and social relationships	14.30±3.76
Self-care	15.70±4.53
Disturbing and aggressive behaviors	17.42±3.45

Values are presented as mean ± standard deviation. SD: Standard deviation; FAB: Frontal Assessment Battery; TALD: Thought and Language Disorder Scale; PSP: Personal and Social Performance Scale; PANSS: Positive and Negative Syndrome Scale.

Psychopathology and functioning scores are summarized in Table 2. The mean PANSS total score was 71.53±16.50, indicating a moderate level of overall symptom severity. The mean PSP total score was 61.64±13.09. Mean PSP subscale scores were 14.22±4.73 for socially useful activities, 14.30±3.76 for personal and social relationships, 15.70±4.53 for self-care, and 17.42±3.45 for disturbing and aggressive behaviors.

Correlation analyses examining demographic and illness-related variables demonstrated no significant associations between PSP total scores and age, education level, duration of illness, duration of untreated psychosis, or number of hospitalizations (all $p > 0.05$). However,

chlorpromazine-equivalent antipsychotic dose showed a moderate positive correlation with the PSP self-care domain ($r = 0.36$, $p < 0.05$).

As shown in Table 3, PSP total scores were negatively correlated with measures of psychopathology and several dimensions of FTD. PSP total scores were negatively correlated with PANSS total ($r = -0.41$, $p = 0.001$), positive symptom ($r = -0.28$, $p = 0.028$), and negative symptom scores ($r = -0.25$, $p = 0.048$). Similar associations were observed across several PSP domains, particularly personal and social relationships and self-care.

Among the TALD dimensions, subjective negative thought disorder demonstrated the strongest and most consistent associations with functional impairment, showing significant negative correlations with PSP total scores ($r = -0.44$, $p < 0.001$), socially useful activities ($r = -0.50$, $p < 0.001$), personal and social relationships ($r = -0.47$, $p < 0.001$), and self-care ($r = -0.36$, $p < 0.01$). Objective negative thought disorder showed a similar but weaker pattern of associations. Objective positive thought disorder was also associated with poorer functioning across several domains, although the correlations were generally less pronounced. In contrast, subjective positive thought disorder was not significantly associated with functional outcomes.

Regarding executive functioning, verbal fluency was positively correlated with overall functioning ($r = 0.32$, $p < 0.05$), socially useful activities ($r = 0.39$, $p < 0.01$), personal and social relationships ($r = 0.31$, $p < 0.05$), and self-care ($r = 0.35$, $p < 0.05$). Sensitivity to interference was positively associated with socially useful activities ($r = 0.35$, $p < 0.01$) and self-care ($r = 0.46$, $p < 0.01$).

As shown in Table 4, a multiple linear regression analysis was conducted to identify factors independently associated with personal and social functioning. Variables that showed significant associations with PSP scores in bivariate analyses and were considered clinically relevant were entered into the model, including PANSS negative symptoms, subjective negative thought disorder, and executive functioning (FAB total score). The overall model was statistically significant ($F = 4.870$, $p = 0.004$), accounting for 19.6% of the variance in PSP total scores ($R^2 = 0.196$, adjusted $R^2 = 0.154$). Subjective negative thought disorder emerged as the only significant independent correlate of poorer functioning ($\beta = -0.324$, $p = 0.032$). Neither PANSS negative symptoms ($\beta = -0.044$, $p = 0.764$) nor executive functioning ($\beta = 0.200$, $p = 0.098$) remained significantly associated with PSP total scores in the multivariate model.

Table 3: Correlations of psychopathology, thought disorder, executive functioning, and functional outcomes

	PSP total	PSP social	PSP personal	PSP self-care
PANSS total score	-0.41**	-0.32**	-0.42**	-0.40**
PANSS positive symptoms	-0.28*	-0.20	-0.31*	-0.27*
PANSS negative symptoms	-0.25*	-0.24	-0.24	-0.26*
TALD objective positive	-0.34**	-0.28*	-0.30*	-0.27*
TALD subjective negative	-0.44***	-0.50***	-0.47***	-0.36**
TALD objective negative	-0.38**	-0.42**	-0.31*	-0.34**
TALD subjective positive	-0.10	-0.10	-0.15	-0.07
FAB conceptualization	-0.23	0.25*	0.09	0.14
FAB verbal fluency	0.32*	0.39**	0.31*	0.35*
FAB sensitivity to interference	0.24	0.35**	0.21	0.46**
FAB inhibitory control	0.07	0.01	-0.01	-0.08

Values are Spearman's rho correlation coefficients. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; TALD: Thought and Language Disorder Scale; FAB: Frontal Assessment Battery; PSP: Personal and Social Performance Scale; PANSS: Positive and Negative Syndrome Scale.

Table 4: Multiple linear regression analysis of factors associated with personal and social functioning (PSP total score)

Predictor	B	SE	Standardized β	t	p
FAB total score	0.747	0.445	0.200	1.681	0.098
PANSS negative symptoms	-0.093	0.310	-0.044	-0.302	0.764
TALD subjective negative	-1.357	0.618	-0.324	-2.194	0.032

Model statistics: $R = 0.442$; $R^2 = 0.196$; Adjusted $R^2 = 0.154$; $F = 4.870$; $p = 0.004$. SE: Standard error; β : Standardized regression coefficient; FAB: Frontal Assessment Battery; TALD: Thought and Language Disorder Scale; PANSS: Positive and Negative Syndrome Scale.

DISCUSSION

The present study investigated the relationships among FTD, executive functioning, and personal and social functioning in patients with schizophrenia and a history of violent offending. Several dimensions of FTD and executive functioning were associated with functional outcomes in bivariate analyses. However, after accounting for negative symptom severity and executive functioning, subjective negative thought disorder emerged as the only variable independently associated with overall functioning. These findings suggest that disturbances in the subjective experience and expression of thought may represent a particularly relevant correlate of real-world functioning in forensic schizophrenia populations.

One of the main findings was the robust association between FTD and impaired functioning. Higher levels of thought disorder were associated with poorer functioning in socially useful activities, interpersonal relationships, and self-care. Among the TALD dimensions, subjective negative thought disorder demonstrated the strongest and most consistent associations across functional domains. These findings are consistent with previous studies showing that FTD contributes substantially to communication difficulties,

impaired social reciprocity, and reduced adaptive functioning in schizophrenia spectrum disorders (17, 31). Disturbances such as impoverished thought expression, difficulties verbalizing internal experiences, and subjective experiences of cognitive fragmentation may interfere with effective communication and social problem-solving, potentially limiting the ability to maintain interpersonal relationships and perform everyday activities (19).

Importantly, subjective negative thought disorder remained independently associated with poorer functioning after accounting for negative symptoms and executive functioning. This finding extends previous research by suggesting that specific dimensions of thought disorder may be associated with disability beyond traditional symptom domains. Although negative symptoms are widely recognized as major correlates of functional outcomes in schizophrenia (3), the present findings indicate that subjective disturbances in thought and language may capture additional aspects of social and behavioral functioning that are not fully accounted for by negative symptom severity. Recent evidence has also demonstrated that objective positive and subjective negative dimensions of FTD are associated with violent offending in schizophrenia (18). Taken together, these

findings suggest that different dimensions of thought disorder may be associated with distinct adverse real-world outcomes, including violent behavior and functional disability.

The relationship between thought disorder and functioning may be particularly relevant in forensic populations. Individuals with severe disturbances in thought organization may experience difficulties interpreting social cues, communicating their needs effectively, and responding adaptively in interpersonal situations. Such impairments may contribute not only to social withdrawal and occupational dysfunction but also to maladaptive responses during stressful or conflictual encounters (5, 32). From this perspective, FTD may represent more than a diagnostic feature of schizophrenia; it may also serve as a clinically meaningful marker of vulnerability to poor social adaptation.

Executive functioning was also associated with functioning at the correlational level. Better verbal fluency was associated with better overall functioning, interpersonal relationships, and self-care, whereas greater cognitive flexibility was associated with better functioning in socially useful activities and self-care. These findings are consistent with previous studies demonstrating that executive processes, including cognitive flexibility, planning, and verbal organization, support social competence and goal-directed behavior in schizophrenia (11, 33). However, overall executive functioning did not remain independently associated with functioning in the multivariate model. This finding suggests that executive deficits may be indirectly related to functioning or may operate through mechanisms that overlap with thought disorder and broader psychopathology, rather than exerting a unique effect on functioning in this population.

Although the regression model was statistically significant, it explained only 19.6% of the variance in personal and social functioning. This finding underscores the multifactorial nature of functional outcomes in schizophrenia and suggests that additional clinical, cognitive, environmental, and psychosocial factors not assessed in the present study are likely to contribute. Variables such as medication adherence, social support, psychosocial stressors, detailed substance use characteristics, and the severity and characteristics of violent behavior may account for some of the unexplained variance.

The observed associations between executive functioning and thought disorder further support the possibility that these constructs share partially overlapping neurocognitive substrates. In particular, verbal fluency and cognitive flexibility were associated

with negative dimensions of thought disorder, consistent with previous evidence linking executive dysfunction, abnormalities in semantic processing, and communication disturbances in schizophrenia (16, 17). Future longitudinal studies incorporating neurocognitive and neurobiological measures may help clarify the mechanisms underlying these relationships.

From a clinical perspective, the present findings highlight the importance of assessing FTD in addition to symptom severity when evaluating functional outcomes in forensic schizophrenia populations. Although antipsychotic treatment remains essential for controlling psychotic symptoms, functional recovery may depend on broader cognitive and communicative capacities. Interventions targeting communication skills, social cognition, cognitive flexibility, and thought organization may therefore be valuable components of comprehensive rehabilitation programs. Incorporating structured assessments of thought disorder into routine clinical and forensic evaluations may also facilitate individualized treatment planning and improve long-term psychosocial outcomes.

Several limitations should be considered when interpreting the findings of this study. First, the cross-sectional design precludes conclusions regarding causal relationships among FTD, executive functioning, and functional impairment. Longitudinal studies are needed to clarify the temporal and potentially bidirectional relationships among these variables. Second, the relatively small sample size and inclusion of only forensic inpatients with a history of violent offending may limit the generalizability of the findings to broader schizophrenia populations. In addition, the absence of a comparison group without a history of violent offending limits conclusions regarding whether the observed associations are specific to this forensic sample. Third, the severity and characteristics of violent offending were not assessed using a standardized violence severity instrument. Therefore, different forms of violent behavior, which may involve distinct neuropsychological and clinical mechanisms, could not be examined separately. Fourth, executive functioning was assessed using the Frontal Assessment Battery, a brief screening instrument, rather than a comprehensive neuropsychological battery. The findings regarding executive functioning should therefore be interpreted cautiously, and broader conclusions regarding executive functioning cannot be drawn. Fifth, psychiatric comorbidities, including personality disorders, were not systematically assessed using a structured diagnostic interview, and intellectual disability was excluded based on clinical

evaluation rather than standardized psychometric testing. These factors may have influenced executive functioning, FTD, and functional outcomes. Finally, several potentially relevant factors, including medication adherence, detailed substance use characteristics, psychosocial stressors, social support, and the severity or frequency of violent behavior, were not evaluated and may have influenced functional outcomes. These unmeasured factors may also partly explain the relatively modest proportion of variance in functioning accounted for by the regression model.

Despite these limitations, the study has several notable strengths. To our knowledge, relatively few studies have simultaneously examined FTD, executive functioning, and personal and social functioning in patients with schizophrenia and a history of violent offending. The use of the Thought and Language Disorder Scale allowed for a multidimensional assessment of both subjective and objective aspects of thought disorder, providing a more nuanced understanding of their relationships with functioning. Furthermore, the inclusion of both PSP total and domain-specific functioning measures enabled the identification of specific areas of functioning associated with thought disorder and executive functioning. Finally, the multivariate analysis identified subjective negative thought disorder as an independent correlate of functional impairment after accounting for negative symptom severity and executive functioning. Together, these findings contribute to a growing body of evidence suggesting that real-world functioning in schizophrenia is associated not only with psychopathology but also with disturbances in thought organization, communication, and cognitive functioning.

CONCLUSION

Formal thought disorder was associated with functional impairment in this forensic sample of patients with schizophrenia and a history of violent offending. Among the clinical and cognitive variables examined, subjective negative thought disorder was the only variable independently associated with personal and social functioning, suggesting that disturbances in the subjective experience and expression of thought may represent an important correlate of real-world disability beyond negative symptom severity and executive dysfunction. These findings highlight the potential value of incorporating detailed assessments of thought disorder into functional evaluation and rehabilitation planning in forensic schizophrenia populations.

Ethical Approval: This study was approved by The Ethics Committee of Ankara Bilkent City Hospital (approval number: 1-24-470, date: 07.08.2024).

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Category 2	Drafting manuscript	G.B.
	Critical revision of manuscript	E.K.S., M.U., G.Z.K.
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Appendix 1: Demographic, clinical, cognitive, and functional characteristics of the forensic schizophrenia sample by sex

Variables	Female (n=17)	Male (n=47)	p
Age (years)	45.29±9.97	38.62±9.61	0.024
Education (years)	10.76±4.51	10.15±3.95	0.623
Duration of untreated psychosis (years)	8.41±11.09	6.36±7.88	0.491
PANSS total score	70.88±17.80	71.77±16.21	0.859
PANSS positive symptoms	17.12±6.72	15.66±5.10	0.424
PANSS negative symptoms	17.00±4.46	18.83±6.60	0.213
CDSS	1.82±1.55	2.57±2.85	0.186
PSP total score	67.06±12.88	59.68±12.74	0.052
FAB total score	13.94±2.63	13.17±3.77	0.366
TALD total score	27.29±9.12	26.98±10.00	0.906

Values are presented as mean±standard deviation. Between-group comparisons were performed using independent-samples t tests. Statistical significance was set at $p<0.05$. TALD: Thought and Language Disorder Scale; FAB: Frontal Assessment Battery; PSP: Personal and Social Performance Scale; PANSS: Positive and Negative Syndrome Scale; CDSS: Calgary Depression Scale for Schizophrenia.



BRIEF REPORT

Primary care physicians' knowledge, attitudes, and clinical practices regarding the management of anxiety and depressive disorders in Georgia

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ABSTRACT

Objective: This study assessed primary care physicians' (PCPs') knowledge, attitudes, self-efficacy, and clinical practices regarding anxiety and depressive disorders in Georgia and identified key barriers to effective care delivery.

Method: A cross-sectional survey was conducted among 78 PCPs in two regions of Georgia using a structured questionnaire that included the Depression Attitude Questionnaire (DAQ). Data were analyzed using chi-square tests and binary logistic regression.

Results: PCPs relied heavily on pharmacotherapy, which was used by 78.2%, whereas fewer than 13% reported using structured psychological interventions. Physicians expressed significantly greater confidence in diagnosing and managing anxiety than depression ($p < 0.001$). Although 65.4% recognized psychotherapy as an effective treatment, 67.9% regarded it as an intervention that should be delivered only by specialists. Female physicians were more than twice as likely to use nonpharmacological interventions than male physicians (odds ratio=2.15, $p=0.019$), despite reporting lower self-confidence.

Conclusion: Primary mental health care in Georgia is constrained by the predominance of pharmacological treatment and low physician self-efficacy. Improving service delivery requires targeted training in psychological interventions, supportive financing mechanisms, and greater multidisciplinary integration.

Keywords: Primary care, anxiety disorders, depressive disorders, psychotherapy

INTRODUCTION

Anxiety and depressive disorders are leading causes of disability worldwide, substantially reducing quality of life and increasing healthcare costs. Despite the availability of effective treatments, these conditions remain underdiagnosed and undertreated, particularly in low- and middle-income countries where access to specialist mental health services is limited (1).

Primary care (PC) is a critical setting for addressing these disorders because of its accessibility and role as the first point within the healthcare system (2, 3). Global strategies, including those promoted by the World Health Organization, emphasize the integration of mental health services into primary care as a scalable and cost-effective approach (4). Evidence from high-income countries indicates that collaborative and stepped-care models can significantly improve patient outcomes (5).

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Successful integration, however, is often hindered by provider-level barriers, including insufficient training, low self-efficacy, and stigma, as well as system-level constraints such as limited consultation time, inadequate financing, and weak referral pathways (6). Consequently, primary care frequently remains dominated by a biomedical model characterized by a strong reliance on pharmacotherapy and limited use of psychological interventions.

These challenges are particularly pronounced in post-Soviet healthcare systems such as Georgia's. Structural reforms have historically prioritized hospital efficiency, while the integration of mental health services into primary care has remained fragmented and specialist-centered (7). Empirical evidence regarding Georgian primary care physicians' (PCPs') knowledge, attitudes, and clinical practices related to mental health care remains limited (8).

This study aimed to assess the knowledge, attitudes, and self-reported clinical practices of PCPs in Georgia regarding anxiety and depressive disorders and to identify key educational and systemic barriers to effective care. By situating the findings within the broader context of health system transformation, the study seeks to inform context-specific reforms and contribute to the international literature on mental health integration in primary care.

METHODS

Study Design and Setting

A cross-sectional survey was conducted between September and December 2025 to assess primary care physicians' knowledge, attitudes, self-efficacy, and clinical practices regarding anxiety and depressive disorders in urban and semi-urban areas of Georgia.

Sampling

Using nonprobability convenience sampling, 103 PCPs were invited to participate, of whom 78 completed the questionnaire, yielding a response rate of 75.7%. Eligible participants were family physicians actively practicing in primary healthcare facilities. Although the sampling method may have introduced selection bias, the sample size was considered sufficient to detect medium effect sizes in an exploratory study.

Data Collection

A structured, self-administered questionnaire assessed four domains: sociodemographic and professional characteristics, knowledge, attitudes, self-efficacy,

and clinical practices. Attitudes were measured using the Depression Attitude Questionnaire (DAQ).

The DAQ was translated into Georgian using a forward-backward translation procedure and was reviewed by experts to ensure cultural appropriateness. A pilot test involving five physicians was conducted to assess clarity. Internal consistency was acceptable, with Cronbach's alpha values ranging from 0.72 to 0.81.

Anonymous paper-based questionnaires were distributed to physicians who voluntarily agreed to participate. To reduce social desirability bias, no personally identifiable information was collected, and participants were assured of confidentiality. No incentives were provided.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics, version 26.0. Descriptive statistics were used to summarize participant characteristics and survey responses. Chi-square (χ^2) tests and Cramer's V were used to examine associations between categorical variables and estimate effect sizes, with values of at least 0.10, 0.30, and 0.50 interpreted as small, medium, and large effects, respectively. Binary logistic regression was used to identify predictors of the use of nonpharmacological interventions. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$.

Ethical Considerations

The study was approved by the Caucasus University Ethics Committee (Protocol No. CU 53-12.01.25) and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent.

RESULTS

The study included 78 PCPs of whom 46 were women and 32 were men. The overall response rate was 75.7%.

Pharmacological approaches predominated. Antidepressants were identified as effective by 79.5% of participants, whereas 62.8% recognized psychotherapy as effective. Perceptions of treatment effectiveness were less consistent for anxiety disorders than for depressive disorders.

A substantial confidence gap was observed between the management of anxiety and depression (Table 1). PCPs reported greater confidence in recognizing and diagnosing anxiety than depression (66.7% vs. 33.3%, $p < 0.001$). They were also more

Table 1: Confidence in clinical practice and gender differences in clinical interventions

Domain/intervention	Total/subgroup	n (%)	p
High level of confidence	Anxiety	Depression	
Recognition and diagnosis	52 (66.7%)	26 (33.3%)	<0.001
Overall management	38 (48.7%)	11 (14.1%)	<0.001
Gender differences in clinical practice	Female (n=46)	Male (n=32)	
Psychoeducation	31 (67.4%)	13 (40.6%)	0.022
Supportive therapy	28 (60.9%)	12 (37.5%)	0.041
Family-oriented care	22 (47.8%)	8 (25.0%)	0.040
Pharmacotherapy	39 (84.8%)	26 (81.3%)	0.681

Female physicians were more likely than male physicians to use non-pharmacological interventions (OR=2.15, 95% CI: [1.12–4.11], p=0.019). Bold values indicate statistical significance (p<0.05).

Table 2: Attitudes of primary care physicians toward the management of depression

Attitudinal statement	Respondents agreeing n (%)
Working with patients with depression is emotionally demanding.	71 (91.0)
Depression is a natural consequence of life stress.	64 (82.1)
Helping patients with depression is more difficult than treating patients with other conditions.	61 (78.2)
Most patients with depression require care from a mental health specialist.	55 (70.5)
Psychotherapy should be provided only by mental health specialists.	53 (67.9)
Psychotherapy is the most effective treatment for depression.	51 (65.4)
Nurses play an important role in the management of depression.	46 (59.0)
Treating depression is an important responsibility of family physicians.	41 (52.6)
Antidepressant medications only mask the symptoms of depression.	32 (41.0)

confident in managing anxiety than depression (48.7% vs. 14.1%, $p<0.001$). Overall, PCPs reported independently managing only 34.6% of patients with anxiety or depressive disorders, while 65.4% were referred to specialists. Pharmacotherapy was the most frequently used intervention, reported by 78.2% of participants. In contrast, structured psychological approaches, including counseling and problem-solving interventions, were used by fewer than 13%.

PCPs expressed ambivalent attitudes toward their role in depression care (Table 2). Although 52.6% regarded the treatment of depression as part of the family physician's role, 70.5% believed that most patients with depression required specialist care. High levels of perceived burden were also reported. A total of 91% described working with depressed patients as demanding.

DISCUSSION

This study identified a consistent pattern of pharmacological dominance, low physician self-efficacy, particularly in depression care, and limited use of psychological interventions within

Georgian primary care. These findings institutional and professional barriers commonly observed in transitional healthcare systems (9).

The strong reliance on pharmacotherapy, despite widespread recognition of the effectiveness of psychotherapy, indicates a substantial implementation gap (10). This pattern suggests the persistence of a biomedical model in which mental disorders are conceptualized primarily as conditions requiring medication. Such an approach is common in post-Soviet healthcare contexts, where mental health services have traditionally been specialist-driven and pathology-oriented.

The marked deficit in self-efficacy related to depression, compared with anxiety, suggests that PCPs perceive depression as more complex and less manageable. This finding is consistent international evidence showing that PCPs often experience difficulty managing the chronic and psychosocial dimensions of depression (11). Low self-efficacy remains an important barrier to integrating mental health care into primary care. Greater confidence in anxiety management may be related to the frequent somatic presentation of anxiety symptoms. In contrast,

effective depression care often requires nuanced communication and longitudinal monitoring, all of which may be difficult to provide during time-limited consultations.

The finding that many PCPs acknowledged a role in depression care while still preferring specialist referral reflects a referral-oriented clinical culture (12). In healthcare systems with weak integration mechanisms, responsibility for mental health care may formally remain within primary care but be functionally transferred to specialists.

Female physicians were significantly more likely to use nonpharmacological approaches, including psychoeducation and supportive therapy, despite reporting lower self-confidence. This finding is consistent with international evidence indicating that female physicians may use more patient-centered communication and psychosocial approaches than male physicians. Its relevance in Georgia, however, is context-specific (13). Within a healthcare system historically dominated by a specialist-centered biomedical model, female PCPs may demonstrate greater behavioral readiness to adopt integrated mental health practices. Their proactive use of psychosocial strategies despite lower perceived confidence suggests that they may serve as early adopters of reform. Consequently, mental health policies in Georgia should build on these gender-specific clinical strengths to support the transition toward a more holistic model of primary care.

System-level barriers, including high patient workloads and the absence of adequate reimbursement mechanisms for mental health services, create structural disincentives for comprehensive care (14). Under these conditions, pharmacotherapy may become the most feasible and readily available intervention. Transitioning to integrated care will require strengthening training in primary care–appropriate psychological interventions and integrating mental health professionals into multidisciplinary primary care teams (15).

The findings demonstrate how global models of mental health integration are shaped by local institutional conditions. Improving mental health service delivery in Georgia requires a dual approach that strengthens physicians' competencies while addressing structural barriers that reinforce pharmacological dominance.

Specifically, introducing performance-based financial incentives for mental health screening and embedding mental health nurses within primary care

teams could help shift the current referral-oriented culture toward integrated care while reducing the workload of individual primary care physicians.

Study Limitations

The cross-sectional study design and convenience sample of 78 participants recruited from only two regions limit the generalizability of the findings and preclude causal inferences. Additionally, the use of self-reported data may have introduced social desirability bias. Despite these limitations, the findings highlight the urgent need for targeted educational initiatives and health system reforms to strengthen mental health care in primary care settings.

CONCLUSION

This study identified important gaps in Georgia's primary mental health services, particularly the persistent reliance on pharmacotherapy and low physician self-efficacy in managing depression. These challenges reflect both individual competency gaps and structural constraints within a transitional healthcare system.

The findings reveal a mismatch between the recognized importance of primary mental health care and PCPs' practical capacity to deliver it. This mismatch is reinforced by a referral-oriented culture and insufficient training in psychosocial interventions. Addressing these challenges requires a coordinated system-level response that prioritizes practical training in primary care–adapted psychological interventions and creates supportive institutional conditions through improved financing, reduced workloads, and the integration of multidisciplinary primary care teams. Ultimately, the successful integration of mental health services into primary care in Georgia will depend on aligning evidence-based models of care with local institutional realities to ensure that policy ambitions translate into effective service delivery.

Ethical Approval: This study was approved by the Research and Ethics Committee of Caucasus University (Approval No. CU 39-21.01.24 – 01.21.2024).

Informed Consent: Written informed consent was obtained from all participants.

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REVIEW ARTICLE

Personality disorders in a non-Western context: A comprehensive meta-analysis of personality disorder prevalence in Türkiye

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ABSTRACT

Personality disorders (PDs) are severe mental health conditions associated with significant distress and functional impairment. However, the epidemiology of personality disorders in non-Western populations is underrepresented. This meta-analysis aimed to estimate the prevalence of any personality disorder in both clinical and community samples in Türkiye. A systematic search was conducted in Web of Science, PubMed, Scopus, TRDizin, and the Turkish Psychiatry Index. The meta-analysis was performed in RStudio following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 49 articles, comprising 61 independent samples and 28,269 participants, were included. The pooled prevalence of any personality disorder across all samples was 26.06% (95% confidence interval (CI) [0.1870, 0.3507]). The pooled prevalence was 30.60% (95% CI [0.2049, 0.4301]) in clinical samples and 15.94% (95% CI [0.1063, 0.2322]) in community samples. The findings indicate that PDs are highly prevalent in both clinical and community settings. These results suggest that PDs represent a substantial public health concern and should not be considered solely within clinical populations.

Keywords: Personality disorders, prevalence, epidemiology, meta-analysis, Türkiye

INTRODUCTION

According to a comprehensive review, the prevalence of any personality disorder (PD) ranges from approximately 2% to 20% in the general population, whereas prevalence estimates in clinical samples are substantially higher, ranging from 40% to 90% in Europe and from 45% to 50% in the United States (1, 2). Gawda reported an overall prevalence of approximately 10% for any PD in community samples (1). In Türkiye, the average prevalence of any

PD diagnosis among psychiatric patients has been reported to be 52% (3). Worldwide, the prevalence of PDs in the general population is estimated to be approximately 9–10% (4, 5). A notable disparity in prevalence estimates has been reported across Asian countries. For example, prevalence was estimated at 2% in India and 60% in Pakistan, (2) highlighting potential cultural differences in the diagnosis and classification of PDs. Despite growing interest in cross-cultural psychiatry, the epidemiology of PDs in non-Western populations remains underrepresented,

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partly because of differences in cultural norms, stigma, and help-seeking behaviors. The presentation and prevalence of PDs vary across cultures, suggesting that cultural factors influence both symptom expression and diagnostic practices. For example, histrionic PD may be overdiagnosed in South American and Mediterranean cultures, where expressive emotional behavior is more culturally normative despite overlapping with diagnostic criteria (1). Conversely, obsessive-compulsive personality disorder (OCPD) has been reported to be more prevalent in Asian countries than in the United States (6). OCPD is the most commonly diagnosed PD in the United States and Australia, avoidant PD in Norway, and schizotypal PD in Iceland (7). One epidemiological study (8) reported that the prevalence of paranoid, schizoid, schizotypal, antisocial, and dependent PDs each ranged from approximately 0.5% to 1% in the general adult population. In a Turkish psychiatric sample, the prevalence of borderline PD (BPD) was 10.2%, followed by histrionic PD (5%), antisocial PD (ASPD; 3.8%), and narcissistic PD (0.95%) (9).

Studies examining psychiatric comorbidity consistently demonstrate a strong association between PDs and other mental disorders, with approximately 45% of psychiatric patients meeting criteria for at least one PD (8, 10, 11). The most common comorbid conditions include mood disorders among individuals with avoidant and dependent PDs, anxiety disorders among those with BPD, substance use disorders (SUDs) among individuals with schizotypal and borderline PDs, and eating disorders among those with histrionic and borderline PDs (12).

One study found that approximately 25% of individuals with SUD met criteria for BPD (11). PDs have been diagnosed in 44% of individuals with alcohol use disorders and in 79% of those with other substance use disorders (13). Similarly, Bowden-Jones et al. (14) reported prevalence rates of 53% among individuals with alcohol use disorders and 37% among those with substance use disorders. Although many individuals initially seek psychological treatment for substance-related problems, PDs are highly prevalent in this population (15).

Despite the growing body of research on PDs across diverse populations and cultural contexts, studies specifically estimating prevalence remain limited. Accurate prevalence estimates are important because PDs represent a significant public health concern due to their high rates of psychiatric comorbidity and their pervasive impact on multiple domains of functioning

(15–17). Although research on PDs has primarily been conducted in clinical settings, community-based studies remain relatively scarce and are often limited by methodological weaknesses or insufficient sample representativeness (18). Furthermore, the considerable variability in prevalence estimates across studies underscores the importance of examining potential moderators, such as age, sample size, and year of publication.

The present meta-analysis aimed to estimate the prevalence of PDs in Türkiye. Specifically, we estimated the prevalence of any PD and individual PD categories separately in clinical and community samples. The following research questions were addressed:

1. What is the overall prevalence of any PD in Türkiye?
2. What is the prevalence of any PD in community-based samples in Türkiye?
3. What is the prevalence of any PD in clinical samples in Türkiye?
4. What are the prevalence estimates for individual PD categories in Türkiye?
5. Do prevalence estimates for any PD differ across psychiatric comorbidity subgroups?

METHODS

Search Strategy and Eligibility Criteria

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix 1) (19, 20). The literature search was performed between February 21 and March 19, 2024, using the Web of Science (WoS), PubMed, Scopus, TRDizin, and Turkish Psychiatry Index databases. The search strategy was designed to maximize sensitivity and capture all relevant studies. The core search term personality disorder was combined with a wildcard (personality disorder*) to identify plural forms and other lexical variations. In WoS, Scopus, and PubMed, the additional search terms Turkey, Turkish, or Türkiye were included. For the Turkish databases, the equivalent wildcard term kişilik bozuk* was used to capture variations in Turkish terminology. Searches in TRDizin and the Turkish Psychiatry Index were conducted using both English and Turkish search terms. Studies were eligible for inclusion if they (a) reported prevalence data for any PD, (b) employed a cross-sectional or longitudinal design, (c) included Turkish adolescents or adults residing in Türkiye (minimum age: 12 years), (d) were published in Turkish or English, and (e) appeared in peer-reviewed journals. Studies were excluded if they

(a) included fewer than 20 participants, (b) focused on highly specific populations (e.g., patients with neurological disorders), (c) were books, review articles, or conference abstracts, or (d) were unavailable in full text. No lower publication year limit was applied. All eligible studies published up to the final search date (March 19, 2024) were considered to ensure comprehensive coverage of the literature. Although the search period extended through 2024, the eligible studies were published between 1996 and 2022.

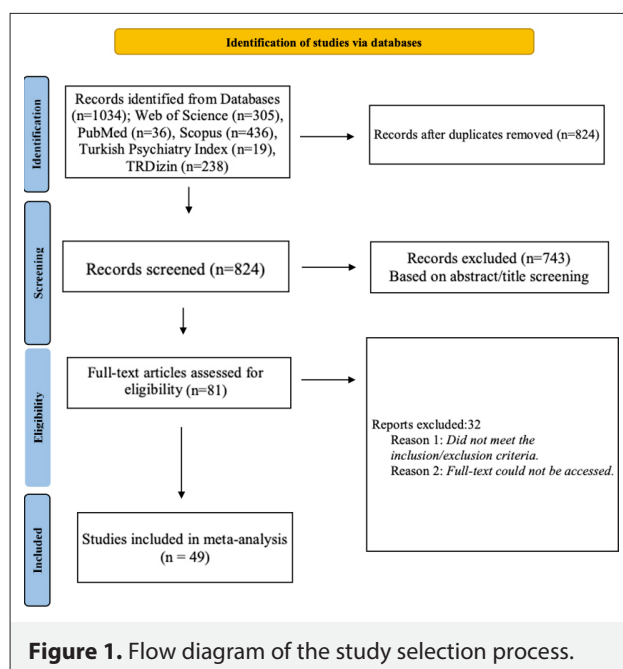
Study Selection Process

The initial database search identified 1,034 records (WoS: 305, PubMed: 36, Scopus: 436, Turkish Psychiatry Index: 19, and TRDizin: 238). After screening according to the eligibility criteria, 49 articles comprising 61 independent samples were included in the meta-analysis. The study selection process is illustrated in Figure 1, and the characteristics of the included studies are summarized in Appendix 2.

Quality Appraisal and Statistical Analysis

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data (21). Each item was scored as 1 ("yes") or 0 ("no" or "unclear"). All included studies achieved a quality score of 6 or higher. All statistical analyses were conducted in RStudio using the metafor and meta packages (22–24). Given the substantial variability across studies in terms of methodology, sampling procedures, diagnostic criteria, inclusion and exclusion criteria, and study populations, pooled prevalence estimates were calculated using a random-effects model with restricted maximum likelihood (REML) estimation (25). In proportional meta-analyses, when study proportions deviate substantially from 0.5 and approach either 0 or 1, statistical challenges arise because these extreme values can receive disproportionate weight in the analysis (26). For this reason, transformation of the effect size estimates is recommended. Although no consensus exists regarding the optimal transformation method, the generalized linear mixed model (GLMM) has been recommended because of its robust statistical performance (27). The GLMM, which assumes a binomial distribution, was implemented in R. Accordingly, the meta-analysis was conducted using a GLMM with a logit transformation.

The prevalence of any PD was estimated for the overall sample and separately for the clinical and community samples. Subgroup analyses were



also conducted to estimate the prevalence of PDs among participants with specific psychiatric comorbidities, including bipolar disorder, substance use disorder, attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and schizophrenia. In addition, pooled prevalence estimates were calculated for each specific PD diagnosis. In proportional meta-analyses, substantial heterogeneity is generally expected because of inherent differences in study populations, settings, and measurement methods (28). Heterogeneity was assessed using Cochran's Q test and the I^2 statistic, which quantify the extent of variability among studies beyond that expected by chance (29). To examine whether the observed heterogeneity was attributable to combining clinical and community samples in a single analysis, subgroup analyses and meta-regression analyses were conducted. Traditional methods for assessing publication bias are generally considered inappropriate for proportional meta-analyses and have been criticized in this context (30). Therefore, publication bias was not formally assessed in the present review.

RESULTS

Study Characteristics

A total of 61 samples from 49 studies comprising 28,269 participants, were included in the meta-analysis. Although passive-aggressive and self-defeating personality disorders (PDs) are not included

in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), these diagnoses were retained because most of the included studies used DSM-III-R criteria. Comorbid diagnostic categories represented by fewer than three samples were excluded from subgroup analyses. The included studies were published between 1996 and 2022. The Structured Clinical Interview for DSM Axis II Personality Disorders (SCID-II) was the most commonly used structured diagnostic interview, whereas one study used the DSM-IV and ICD-10 Personality Questionnaire (DIP-Q) (31, 32).

The included studies comprised both clinical ($n=25,065$) and community ($n=2,894$) samples. Participants ranged in age from 15 to 80 years, and mean ages across studies ranged from 21.4 to 46.3 years (Appendix 2). Clinical samples consisted of psychiatric outpatients and inpatients with a variety of diagnoses. Community samples predominantly included university students, adults from the general population, pregnant women or mothers of infants, and members of several occupational groups. The inclusion criteria varied substantially according to the primary aim of each study. For example, alcohol dependence was an inclusion criterion in studies focusing on substance use disorders. Accordingly, participants were recruited from clinical or community settings appropriate to the objectives of the individual studies. Retrospective studies based on hospital records were also included. Forensic cases derived from forensic hospital records were categorized as clinical samples. All included studies assessed PDs through interviews conducted by psychiatrists. Sex distributions and age-related eligibility criteria varied according to the aims of the individual studies. Detailed study characteristics are presented in Appendix 2.

Pooled Prevalence of Personality Disorders

A total of 61 samples were analyzed to estimate the pooled prevalence of any PD in Türkiye (Appendix 3). In clinical samples, the pooled prevalence of any PD was 30.60% (95% confidence interval (CI) [0.2049, 0.4301]; $I^2=98.2\%$, $Q=2393.16$, $p<0.001$). In community samples, the pooled prevalence was 15.94% (95% CI [0.1063, 0.2322]; $I^2=93\%$, $Q=215.45$, $p<0.05$). Across all samples, the pooled prevalence of any PD was 26.06% (95% CI [0.1870, 0.3507]; $I^2=97.8\%$, $Q=6247.72$, $p<0.001$). The difference in prevalence between clinical and community samples was statistically significant ($p<0.05$).

Pooled prevalence and heterogeneity estimates for individual PD diagnoses were calculated across 36

samples. The pooled prevalence of paranoid PD was 3.58% (95% CI [0.0185, 0.0680]; $I^2=79.9\%$, $Q=173.82$, $p<0.01$). The prevalence of schizoid PD was 0.23% (95% CI [0.0005, 0.0105]; $I^2=75.9\%$, $Q=132.70$, $p<0.01$), and prevalence of schizotypal PD was 2% (95% CI [0.0106, 0.0303]; $I^2=79\%$, $Q=152.5403$, $p<0.01$). The pooled prevalence of ASPD was 1.08% (95% CI [0.0032, 0.0353]; $I^2=81\%$, $Q=184.51$, $p<0.01$). BPD had pooled prevalence of 5.65% (95% CI [0.0342, 0.0920]; $I^2=83\%$, $Q=206.27$, $p<0.01$), whereas the prevalence of histrionic PD was 2.48% (95% CI [0.0130, 0.0466]; $I^2=76.2\%$, $Q=134.70$, $p<0.01$). The pooled prevalence of narcissistic PD was 0.9% (95% CI [0.0017, 0.0215]; $I^2=86.8\%$, $Q=243.04$, $p<0.01$). Avoidant personality disorder (AvPD) had a pooled prevalence of 7.51% (95% CI [0.0496, 0.1121]; $I^2=88.6\%$, $Q=332.30$, $p<0.01$). The prevalence of dependent PD was 2.92% (95% CI [0.0187, 0.0452]; $I^2=3.4\%$, $Q=63.55$, $p<0.01$). The pooled prevalence of OCPD was 8.66% (95% CI [0.0576, 0.1281]; $I^2=85.2\%$, $Q=250.80$, $p<0.01$). The prevalence of passive-aggressive PD was 3.45% (95% CI [0.0212, 0.0556]; $I^2=77.1\%$, $Q=130.99$, $p<0.01$), and the prevalence of self-defeating PD was 1.18% (95% CI [0.0029, 0.0465]; $I^2=69.9\%$, $Q=29.89$, $p<0.01$).

Subgroup Analysis

A sufficient number of samples was available to conduct subgroup analyses by psychiatric comorbidity only for the prevalence of any PD ($n=53$). Across these samples, the pooled prevalence of any PD among participants with comorbid psychiatric disorders was 22.70% (95% CI [0.1556, 0.3187]; $I^2=97.8\%$, $Q=2327.84$, $p<0.001$) (Appendix 4). When the subgroups were examined, heterogeneity was low for the OCD subgroup ($I^2=20.6\%$, $Q=5.04$, $p=0.28$) and the schizophrenia subgroup ($I^2=0\%$, $Q=1.19$, $p=0.55$). In contrast, heterogeneity was substantial in the bipolar disorder ($I^2=97.5\%$, $Q=121.76$, $p<0.01$), SUD ($I^2=94.5\%$, $Q=201.68$, $p<0.01$), suicide attempt ($I^2=98.8\%$, $Q=255.05$, $p<0.01$), and ADHD ($I^2=89\%$, $Q=18.17$, $p<0.01$). The pooled prevalence of any PD was 8.25% in the bipolar disorder subgroup (95% CI [0.0263, 0.2304]), 41.38% in the SUD subgroup (95% CI [0.2989, 0.5389]), 47.53% in the suicide attempt subgroup (95% CI [0.1347, 0.8405]), 46.75% in the OCD subgroup (95% CI [0.3967, 0.5396]), 27.74% in the ADHD subgroup (95% CI [0.0804, 0.6276]), and 73.55% in the schizophrenia subgroup (95% CI [0.6605, 0.7989]). The differences in prevalence across psychiatric comorbidity subgroups were statistically significant ($p<0.001$).

Meta-Regression Analyses

Meta-regression analyses were conducted to investigate potential sources of overall heterogeneity. Mean age did not significantly explain the observed heterogeneity ($Q=1.2900$, $df=1$, $p=0.2561$). Publication year also did not have a statistically significant effect ($Q=3.3032$, $df=1$, $p=0.0691$). In contrast, sample size significantly explained variation across samples ($Q=18.6159$, $df=1$, $p<0.001$).

DISCUSSION

This meta-analysis synthesized data from 61 samples comprising 28,269 participants. The overall pooled prevalence of any PD was 26.06%. It is important to emphasize that the reported prevalence of 26.06% does not represent the prevalence of personality disorders in the general population of Türkiye. Rather, it reflects the pooled prevalence across both community and clinical samples included in this meta-analysis. Nevertheless, the estimate exceeds the DSM-5 general-population prevalence estimate of 9.1% (4). In contrast to Lenzenweger (16), the discrepancy between prevalence estimates may suggest that DSM-based figures underestimate the true burden of personality disorders. However, this interpretation cannot be confirmed without evidence that the included studies were methodologically rigorous and representative of the underlying population.

High heterogeneity observed across all included studies ($I^2=98.2\%$) may reflect methodological differences among the studies. A qualitative synthesis showed that most studies used the SCID-II as the diagnostic instrument and DSM-III-R as the diagnostic criteria. Although the studies contributing to the high heterogeneity were not methodologically identical, the variation in prevalence estimates is unlikely to be explained solely by methodological differences related to sample representativeness. To explore potential sources of heterogeneity, three separate meta-regression analyses were conducted. Mean age was not significantly associated with heterogeneity in the overall meta-analysis. The publication year also did not reach statistical significance, although the result approached the conventional threshold ($Q=3.3032$, $p=0.0691$), suggesting that temporal changes over the approximately 25-year study period may warrant further investigation. Sample size, however, significantly explained variation across studies ($Q=18.6159$, $p<0.001$). In large prevalence meta-analyses, the I^2 statistic may be inflated because

large total sample sizes reduce within-study sampling error ($n=28,269$). Accordingly, the high heterogeneity observed in this review should not be interpreted solely as evidence of methodological weakness. It may also reflect genuine clinical variability arising from the inclusion of general-population cohorts and participants with diverse psychiatric conditions. Despite this heterogeneity, the present review provides the first comprehensive synthesis of PD prevalence across clinical and community samples in Türkiye.

The observed variation in prevalence estimates across studies is consistent with Gawda's assertion that the prevalence of personality disorders differs across cultural contexts (1). The reported prevalence of personality disorders in the general population ranges from 2% to 20% across the United States, Africa, Europe, Asia, and Australia (1, 33, 34). The pooled prevalence of 26.06% observed in the present meta-analysis appears to be slightly higher than this reported range. This finding may suggest that personality disorders are more prevalent in Türkiye; however, such an interpretation should be made cautiously because of substantial methodological and cultural differences across studies. The relatively high prevalence observed in Türkiye may also be influenced by the diagnostic criteria used, particularly given the limited number of personality disorder studies conducted in the country. Clemente et al. (6) reported that DSM-III criteria yielded lower diagnostic rates than other diagnostic systems. The high pooled prevalence is particularly noteworthy, given that most included studies used DSM-III or DSM-III-R diagnostic criteria. This finding highlights the need to consider the potential for overdiagnosis when interpreting prevalence estimates.

A systematic review of general-population studies in Western countries reported an overall PD prevalence of approximately 9% (35). These lower prevalence estimates appear inconsistent with concerns that studies using DSM-III-R may overdiagnose personality disorders. According to a global meta-analysis (36), the worldwide prevalence of personality disorders typically ranges from 5% to 10%. The findings of the present meta-analysis suggest that the prevalence of personality disorders in Türkiye may be higher than the global estimate. Therefore, additional methodologically homogeneous studies are needed to determine whether the prevalence of personality disorders in Türkiye is truly higher than that reported in other populations.

Fewer community samples were available than clinical samples. Globally, prevalence studies are conducted less frequently in community populations than in clinical samples (18). The pooled prevalence of any personality disorder in community samples was 15.94%, which was lower than that observed in clinical samples. A meta-analysis of community-based studies reported a prevalence of 7.8% (36), whereas another review estimated the prevalence at 10% (1). These findings suggest that prevalence estimates from Turkish community samples may be slightly higher than those reported in the international literature. The results also indicate that the prevalence of any PD varies according to sample characteristics. The prevalence of any PD was significantly higher in clinical samples than in community samples. However, because relatively few meta-analyses have examined prevalence across both clinical and community populations, direct comparisons remain limited. This underscores the contribution of the present study to a more integrated understanding of PD prevalence. According to a previous meta-analysis of individuals with psychiatric diagnoses in Türkiye, the prevalence of any PD was 52% (3). In the present meta-analysis, the pooled prevalence of any PD among comorbid diagnostic groups was 22.70% across 53 samples. Several methodological differences may explain this discrepancy. Most notably, Dereboy et al. (3) included only studies that used the SCID-II, whereas the present review also included studies that used other validated assessment instruments. Additionally, the inclusion and exclusion criteria were broader in the present meta-analysis. Consequently, the greater methodological diversity likely contributed to the relatively high heterogeneity observed. The broader scope of this review also allowed the inclusion of a more diverse range of samples, which may have contributed to the differences in PD prevalence estimates compared with the previous meta-analysis. The divergence between the findings of these two meta-analyses, conducted within a relatively short period in the same country, underscores the need for further research.

According to the findings, the highest prevalence of any PD was observed in the schizophrenia subgroup (73.55%), whereas the lowest prevalence was found in the suicide attempt subgroup (7.53%). The comparatively low prevalence in the suicide attempt subgroup may reflect cultural factors related to mental health, such as accessibility to services and stigma. Heterogeneity was low in the schizophrenia subgroup, suggesting that the findings were relatively

consistent across studies. Given the high prevalence of PDs in this subgroup, these findings underscore the importance of routinely screening individuals with schizophrenia for comorbid PDs. Furthermore, previous evidence suggests that not only individuals with schizophrenia but also their relatives are at increased risk of PDs (4). Overall, the prevalence of any PD differed significantly across comorbid diagnostic subgroups ($p < 0.0001$), indicating that individuals with schizophrenia were more likely to have a comorbid PD than those with a history of suicide attempts or the other comorbid conditions examined in this review.

The prevalence of 12 personality disorder diagnostic categories was examined in the clinical, community, and total samples. In the total sample, schizoid PD had the lowest prevalence (0.23%), whereas OCPD had the highest prevalence (8.66%). For all PD diagnoses that could be compared across clinical and community samples, prevalence was consistently lower in community samples than in clinical samples. Because the prevalence of schizotypal PD could only be estimated for the total sample, it could not be included in this comparison. Overall, heterogeneity tended to be lower in community samples than in clinical samples. Within the clinical sample, schizoid PD had the lowest prevalence (0.49%), whereas ASPD had the lowest prevalence in the community sample (0.15%). The prevalence of schizoid personality disorder in the total sample was also comparable to that of ASPD (0.19%).

Among the personality disorders most frequently reported in the literature are AVPD and BPD (7, 16). In the present meta-analysis, OCPD had the highest prevalence, followed by AVPD (7.51%) and BPD (5.65%). In a previous study conducted in Türkiye, the prevalence of BPD in a psychiatric sample was reported to be 10.2% (9). In the present review, conducted 27 years later, the prevalence of BPD in clinical samples was 9.86%. The prevalence of BPD appears to have remained relatively stable over time in both clinical and general populations. The slight difference between the two estimates may reflect changes in diagnostic practices or shifts in population characteristics over time. The prevalence of BPD observed in the present review (9.86%) is also very close to, although slightly lower than, the DSM-5 estimate for clinical populations (10%) (5). Overall, the prevalence of individual PD diagnostic categories ranged from 0.19% to 11.9%. Because PDs are chronic conditions that adversely affect multiple domains of functioning, they represent not only an individual clinical concern but also an important public health issue.

High heterogeneity was observed in many analyses, which is expected in proportional meta-analyses because of the inherent variability among prevalence studies. Although this review adhered to the PRISMA guidelines, the study protocol was not prospectively registered in a public registry such as PROSPERO. The absence of prospective registration represents a limitation in terms of review transparency. However, to minimize the risk of post hoc analytical decisions and selective reporting, all eligibility criteria, quality appraisal procedures, and statistical analysis plans were established before data extraction and implemented without deviation. Despite an extensive database search, no specific efforts were made to identify unpublished studies. Publication bias was not assessed because conventional methods for evaluating publication bias are not considered appropriate for proportional meta-analyses, as described in the Methods section. This represents a limitation of the present review. However, to minimize the risk of bias, a standardized study quality appraisal tool was applied, and no substantial methodological concerns were identified. Another limitation is that the literature search was restricted to Web of Science, PubMed, Scopus, TRDizin, and the Turkish Psychiatry Index. Comprehensive repositories of academic dissertations, such as the Turkish Higher Education Council National Thesis Center and ProQuest, were not searched. The exclusion of these sources represents a methodological limitation, as it may have resulted in the omission of relevant local research, including unpublished master's and doctoral dissertations, thereby increasing the risk of publication bias. Consequently, the pooled prevalence estimates may be slightly inflated if studies reporting non-significant or null findings were less likely to be published in peer-reviewed journals. Although the primary objectives of the included studies varied, all were retained because they reported valid prevalence estimates for PDs. Another methodological limitation relates to the search strategy. The literature search relied primarily on the term *personality disorder**, without explicitly incorporating the names of individual PD subtypes (e.g., *borderline personality disorder*, *antisocial personality disorder*, *narcissistic personality disorder*, or *obsessive-compulsive personality disorder*) or relevant diagnostic codes. Although subsequent sensitivity searches using subtype-specific keywords did not identify any additional eligible studies, this search strategy may nevertheless have introduced a theoretical risk of selection bias. In particular, this approach may have excluded regional publications

that focused exclusively on a single personality disorder subtype without indexing or referencing the broader term *personality disorder* in the title, abstract, or keywords. Nevertheless, the primary objective of this review was to estimate the prevalence of any PD. Another important limitation concerns the demographic composition of the included samples. Because community samples were not fully representative of the broader Turkish population, the estimated community prevalence (16%) may not be generalizable to older adults, rural populations, or other underrepresented groups. Finally, difficulties were encountered when transforming the data for schizotypal personality disorder, preventing separate subgroup analyses for clinical and community samples. As specified in the predefined eligibility criteria, only studies reporting the prevalence of any PD were included. Future systematic reviews and meta-analyses focusing on individual PD diagnoses may provide more robust prevalence estimates for schizotypal personality disorder.

CONCLUSION

Determining the prevalence of personality disorders is important because of their chronic and pervasive nature. As PDs are typically diagnosed using diagnostic manuals and assessment instruments developed in Western cultural contexts, questions remain regarding their cross-cultural applicability. In addition, individual prevalence studies are often limited by issues of representativeness. Consequently, proportional meta-analyses provide an important means of synthesizing the available evidence. The findings of this meta-analysis suggest that the overall pooled prevalence of PDs in Türkiye (26.06%) is relatively high compared with estimates reported in the literature. When examined by sample type, the prevalence was higher in clinical samples (30.60%), as expected given patterns of help-seeking behavior. However, the prevalence observed in community samples (15.94%) also appears higher than that reported in previous studies of non-clinical populations. This finding suggests that PDs represent a significant public health concern and should not be considered solely within clinical settings. Furthermore, high rates of PD comorbidity were observed in specific diagnostic groups, particularly among individuals with schizophrenia, OCD, and SUD. Although the existing literature indicates that personality disorders are highly prevalent, further prevalence studies and meta-analyses are needed to strengthen the evidence base.

Online Appendices Files: <https://dusunenadamdergisi.org/storage/upload/files/1787827400-appendix-en.pdf>

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Category 1	Concept/Design	D.N.C.O., O.Y.A.
	Data acquisition	D.N.C.O.
	Data analysis/Interpretation	D.N.C.O.
Category 2	Drafting manuscript	D.N.C.O.
	Critical revision of manuscript	O.Y.A.
Category 3	Final approval and accountability	D.N.C.O., O.Y.A.
Other	Technical or material support	D.N.C.O.
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LETTER TO THE EDITOR

Duloxetine-associated recurrent angioedema: A dechallenge–rechallenge case

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Dear Editor,

Duloxetine is a selective serotonin–norepinephrine reuptake inhibitor (SNRI) widely used in the treatment of major depressive disorder, anxiety disorders, neuropathic pain syndromes, and fibromyalgia (1). Its safety profile has been well documented, with commonly reported adverse effects including nausea, diarrhea, dizziness, hypertension, and palpitations (2). However, rare hypersensitivity reactions, including angioedema and other severe cutaneous reactions, have been described in association with duloxetine use (3). Here, we report a case of angioedema temporally associated with duloxetine exposure in which dechallenge and rechallenge findings suggest a probable drug-related reaction.

The patient was a 56-year-old woman whose psychiatric symptoms began during her university years and included insomnia, anhedonia, reduced motivation, and prominent somatic complaints. Regular psychiatric follow-up was initiated in 2021 because of progressively worsening anxiety and depressive symptoms. Amitriptyline was maintained for approximately four years with good tolerability; however, because of weight gain and hypersomnia, it was gradually tapered and discontinued before initiation of duloxetine. Duloxetine was started in September 2024 at 30 mg/day and increased to 60 mg/day after partial clinical improvement, with Beck Depression Inventory (BDI) scores decreasing from 31 at baseline to 23 before the onset of angioedema.

Approximately seven months after treatment initiation, the patient developed unilateral swelling of the right lip and cheek accompanied by mild swallowing discomfort without respiratory compromise. She presented to the emergency department, where intravenous corticosteroids and antihistamines provided transient partial relief. Physical examination revealed localized non-pitting facial edema without urticaria, mucosal or upper airway involvement, wheezing, or dermographism. Over the following three months, recurrent episodes occurred, with progressive extension of edema and diminishing response to treatment.

Dermatologic evaluation established a diagnosis of angioedema. The patient had no history of autoimmune or lymphoproliferative disease, thyroid dysfunction, or prior hypersensitivity conditions, and no family history suggestive of hereditary angioedema. Laboratory investigations—including C1q, C1 esterase inhibitor levels, complement C4, total immunoglobulin E, and peripheral eosinophil count—were within normal limits. These findings were considered sufficient to exclude hereditary or bradykinin-mediated angioedema. No exposure to medications or conditions commonly associated with drug-induced angioedema, including angiotensin-converting enzyme inhibitors, aspirin, opioids, recent infection, food allergens, or herbal supplements, was identified.

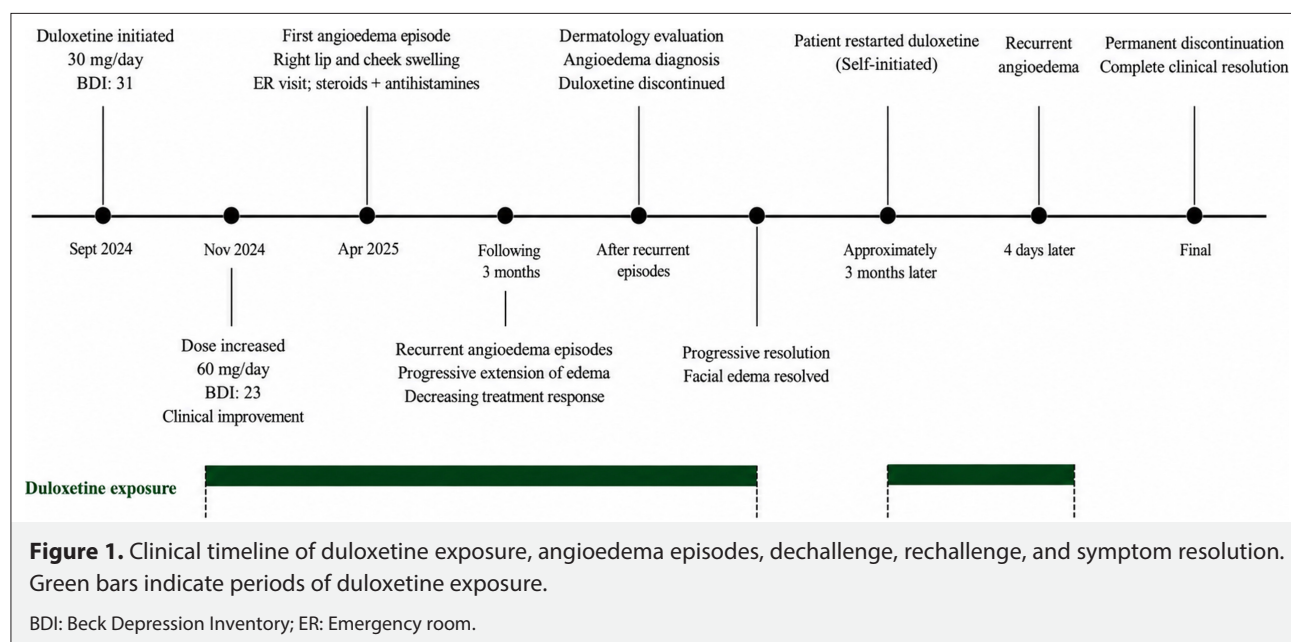
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Duloxetine was discontinued under psychiatric supervision, resulting in progressive resolution of facial edema. Approximately three months later, the patient independently restarted duloxetine because of persistent depressive symptoms. Facial swelling recurred within four days in the absence of any identifiable trigger. Repeat dermatologic evaluation confirmed duloxetine-associated angioedema, and permanent discontinuation of duloxetine led to complete clinical resolution. The clinical course of duloxetine exposure and angioedema episodes is summarized in Figure 1.

Angioedema is characterized by localized, transient swelling of subcutaneous or submucosal tissues caused by increased vascular permeability (4). It most commonly affects the face, lips, oropharynx, and extremities. Various drugs, foods, insect stings, and chemical agents have been reported as triggers (5, 6). Angioedema may arise through several pathophysiological mechanisms, most commonly histamine-mediated mast cell activation or bradykinin-mediated pathways. Histamine-mediated forms result from mast cell degranulation and release of vasoactive mediators, whereas bradykinin-mediated angioedema is related to dysregulation of the kallikrein-kinin system and accumulation of bradykinin, a potent vasoactive peptide that promotes vasodilation and tissue edema. In drug-induced cases, additional idiosyncratic immune or neurovascular mechanisms have also been proposed (7).

Although angioedema is not commonly listed among the adverse effects of SNRI medications, isolated cases associated with duloxetine and venlafaxine have

been reported (8, 9). Similar reactions have also been described with other serotonergic antidepressants, and increased peripheral serotonin concentrations, as well as immune-mediated mechanisms, have been proposed as potential contributors to antidepressant-associated urticaria and angioedema (10).

Although the precise mechanism underlying duloxetine-associated angioedema remains unclear, the absence of urticaria together with only partial response to antihistamines in our patient may suggest a non-histaminergic pathway. Symptom resolution following duloxetine discontinuation, recurrence after re-initiation, and exclusion of alternative etiologies support a drug-related association between duloxetine and angioedema. The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 8, indicating a “probable” adverse drug reaction, while the rapid recurrence after rechallenge may be compatible with a sensitization-related hypersensitivity mechanism.

This case highlights a rare but clinically relevant adverse reaction and emphasizes the importance of considering medication-related causes in patients presenting with late-onset angioedema during otherwise stable antidepressant therapy.

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LETTER TO THE EDITOR

Lower lumbar and sacral herpes zoster with central nervous system complications: Two case reports

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Dear Editor,

Herpes zoster rarely involves the lower lumbar or sacral dermatomes and only infrequently results in neurological complications such as aseptic meningitis or encephalitis, particularly in immunocompromised individuals (1, 2). We report two cases of neurological complications associated with herpes zoster involving uncommon dermatomes. These cases highlight that varicella-zoster virus (VZV) infection in atypical dermatomes may be complicated by central nervous system (CNS) disease, even in the presence of normal neuroimaging findings. They also underscore the critical role of cerebrospinal fluid (CSF) polymerase chain reaction (PCR) testing in establishing the diagnosis in both immunocompromised and immunocompetent patients presenting with unexplained neurological symptoms.

Case 1: A 68-year-old man with end-stage renal disease who had been receiving hemodialysis for two years presented with a three-day history of speech disturbance. Two days before admission, he experienced dizziness, syncope, and a fall. One week earlier, he had developed a vesicular rash involving the left buttock and thigh (L2–L5 dermatomes), which had been treated with oral acyclovir. On physical examination, the patient was mildly disoriented, had no neck stiffness, and exhibited drying vesicular

lesions (Fig. 1a–c). Laboratory investigations revealed a C-reactive protein (CRP) level of 50 mg/L, a white blood cell (WBC) count of 5,700/μL (lymphocytes: 900/μL), creatinine level of 7.56 mg/dL, a urea level of 135 mg/dL, and a platelet count of 167,000/μL. Testing for antibodies to human immunodeficiency virus (HIV) was negative. Brain imaging, electroencephalography (EEG), and fundoscopic examination were unremarkable. Lumbar puncture demonstrated a CSF protein concentration of 46 mg/dL, a glucose level of 48 mg/dL (serum glucose: 101 mg/dL), and 65 cells/mm³ (98% mononuclear cells). Multiplex PCR testing was positive for varicella-zoster virus, confirming the diagnosis of VZV encephalitis. Cerebrospinal fluid cultures were negative. The patient received intravenous acyclovir (350 mg/day) for seven days, followed by valacyclovir (500 mg/day) for an additional seven days, resulting in complete neurological recovery. Written informed consent for publication of this report and the accompanying images was obtained from both patients.

Case 2: A 47-year-old man with a history of chronic anxiety disorder treated with fluoxetine, venlafaxine, and alprazolam presented with a five-day history of severe bilateral temporal headache accompanied by insomnia, loss of appetite, dizziness aggravated by movement, and photophobia. He had no previous history of headaches. Physical examination revealed

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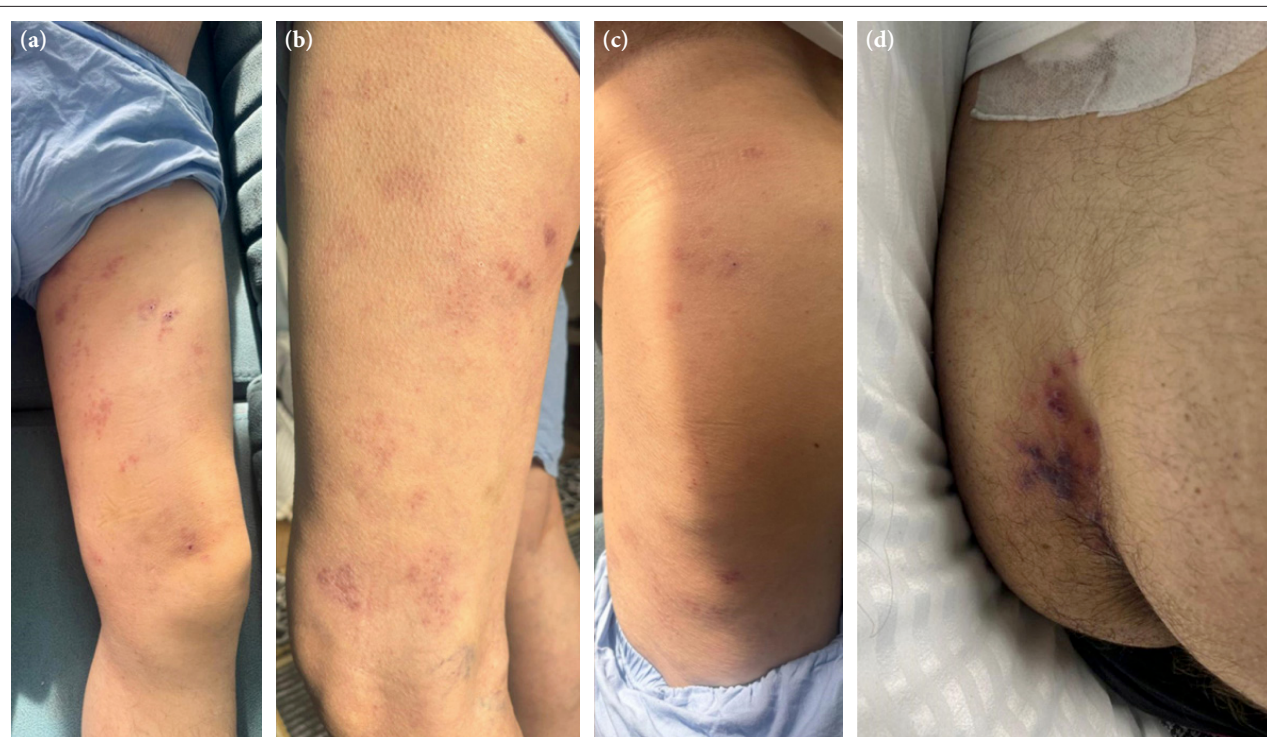


Figure 1. (a–c) Case 1: A 68-year-old man presenting with vesicular lesions involving the medial and lateral aspects of the left thigh and the ipsilateral buttock after approximately one week of oral acyclovir treatment. **(d) Case 2:** A 47-year-old man with sacral vesicular lesions that remained unrecognized until hospital admission following a five-day history of headache. The dressing visible above the lesions corresponds to the lumbar puncture site.

preserved consciousness with neck stiffness, whereas Kernig's and Brudzinski's signs were absent. Vesicular lesions were observed in the sacral S2–S3 dermatomes (Fig. 1d). Laboratory investigations showed a WBC count of 14,400/ μ L and a CRP level of 2.3 mg/L. HIV testing was negative. Brain magnetic resonance (MR) imaging, including diffusion-weighted and contrast-enhanced sequences, MR venography, and fundoscopic examination were unremarkable. CSF analysis revealed an opening pressure of 25 cm H₂O, a protein concentration of 236 mg/dL, a glucose level of 57 mg/dL (serum glucose: 113 mg/dL), and 187 lymphomononuclear cells/mm³. Cerebrospinal fluid cultures were negative. Multiplex PCR testing confirmed varicella-zoster virus infection, establishing the diagnosis of VZV meningitis associated with S2–S3 shingles. The patient was treated with intravenous acyclovir (750 mg three times daily) for 10 days and recovered completely.

The typical clinical presentation of herpes zoster consists of pain accompanied by a vesicular rash, most commonly involving the thoracic and upper lumbar dermatomes (1, 2). Sacral and lower lumbar involvement is relatively uncommon, accounting

for approximately 4–8% of cases (1–3). Herpes zoster involving the cranial and cervical dermatomes (e.g., trigeminal, head, and neck dermatomes) is associated with a higher risk of CNS complications than thoracic involvement (1, 2). Motor and autonomic complications, such as paresis or urinary retention, are uncommon overall but occur more frequently in sacral dermatomes (1–3). In both of our patients, lower lumbar or sacral involvement was present without significant motor or autonomic sequelae.

Multidermatomal herpes zoster is also an uncommon presentation that often suggests an underlying immunosuppressive state, although it may occur in immunocompetent individuals as well (3, 4). In our first patient, involvement of multiple adjacent dermatomes was observed in the setting of significant immune dysfunction.

Varicella-zoster virus meningitis is more commonly reported in younger individuals, whereas VZV encephalitis occurs more frequently in older adults (5, 6). Our cases were consistent with this age-related pattern. Delayed initiation of antiviral therapy has been identified as an important risk factor for CNS involvement in herpes zoster (1). Chronic kidney disease

and hemodialysis are known to impair immune function through mechanisms related to uremia and chronic inflammation, thereby increasing susceptibility to infections (7). Consequently, although our first patient was not receiving conventional immunosuppressive therapy, he was immunocompromised because of end-stage renal disease and long-term hemodialysis. CSF findings in VZV central nervous system infection typically include lymphocytic pleocytosis, elevated protein concentrations, and normal or mildly decreased glucose levels, although atypical presentations and cases without rash have also been reported (8-10). In both patients, the diagnosis was established by CSF PCR testing despite normal neuroimaging and EEG findings (11). Although asymptomatic detection of VZV DNA in the CSF has been reported in both immunocompetent and HIV-positive individuals (11), the clinical presentation and complete response to therapy strongly support true CNS involvement in our cases.

These cases highlight that herpes zoster involving uncommon dermatomes, such as the lower lumbar and sacral regions, may be complicated by serious CNS manifestations, even in the absence of characteristic neuroimaging abnormalities. Clinicians should maintain a high index of suspicion for VZV infection in patients presenting with atypical headaches or unexplained neurological symptoms in the setting of herpes zoster. Prompt CSF PCR testing and early initiation of antiviral therapy remain essential to achieving favorable outcomes, particularly in patients with impaired immune function.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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LETTER TO THE EDITOR

Revisiting clozapine-induced mania: When a case report informs clinical decisions

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Dear Editor,

We write to express our gratitude to Dusunen Adam Journal of Psychiatry and Neurological Sciences and, in particular, to Oğuz et al. (1) for their 2014 case report, “Mania Possibly Induced by Clozapine”. Their report described a rare and clinically counterintuitive adverse reaction that subsequently proved directly relevant to our own clinical reasoning.

Our multidisciplinary team encountered a patient with schizophrenia who developed hypomanic symptoms shortly after clozapine was re-initiated. The patient had no previously documented history of mania or hypomania, and the temporal association between clozapine titration and symptom onset prompted a broad differential diagnostic evaluation. Available investigations did not identify a toxic-metabolic, neurological, or substance-induced explanation, and the phenomenology was more consistent with hypomania than with psychotic exacerbation or behavioral disinhibition. Faced with this unusual presentation, we searched the literature and identified the report by Oğuz et al. (1), which provided a valuable precedent for considering clozapine itself as a potential contributor. Further clinical details, diagnostic considerations, and treatment outcomes from our case have been described in our published Psychopharmacology for the Clinician column in the Journal of Psychiatry and Neuroscience (2).

Although second-generation antipsychotics are generally used to treat mania, they have occasionally been associated with manic or hypomanic switches, primarily in case reports and case series, possibly reflecting their complex neuropsychopharmacological properties (3). In our case, the report by Oğuz et al. (1) was clinically valuable because it highlighted a rare but plausible adverse drug reaction and proposed a potential receptor-level explanation involving serotonergic and dopaminergic mechanisms. Guided by this insight, we reconsidered our differential diagnosis and elected to continue clozapine uptitration to offset the dopamine binding profile observed at lower doses. The patient's condition subsequently stabilized, allowing clozapine treatment to continue at a higher dose.

Recognizing the educational value of this encounter, we subsequently published a detailed report examining the potential manicogenic properties of clozapine (2). Additional recent literature, although sparse, has also described mania-like symptoms temporally associated with clozapine initiation in patients with schizophrenia (4). These observations are clinically important because clozapine is widely regarded as the gold-standard treatment for treatment-resistant schizophrenia and, in selected cases, as a treatment option for severe or refractory bipolar disorder (5–8). This clinical reputation may lower suspicion of clozapine as a potential contributor when new-onset mood elevation occurs, particularly when

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the presentation is initially attributed to psychotic activation, behavioral disinhibition, substance use, or the natural course of the illness.

Mechanistically, this apparent paradox is plausible because clozapine has a complex pharmacodynamic profile whose clinical effects may vary across dose ranges (5, 9). At lower doses, serotonergic effects, including 5-HT_{2A} and 5-HT_{2C} antagonism, may enhance dopaminergic transmission in corticolimbic circuits. Oğuz et al. (1) also discussed possible contributions from D₄ receptor dysregulation and downstream noradrenergic activation. In addition, norclozapine, clozapine's major metabolite, has pharmacological properties that may further complicate the net clinical effect, including partial agonism at D₂/D₃ receptors and activity at muscarinic receptors (10). These mechanisms remain hypothetical and should not be overinterpreted on the basis of individual cases. Nevertheless, they provide biological plausibility for the observation that a medication with established antipsychotic effects, and one that may be clinically useful in manic states, could in rare circumstances be associated with manic or hypomanic excitation.

Our experience highlights three points:

1. Case reports remain valuable when the phenomena in question are rare, paradoxical, and unlikely to be adequately characterized in randomized trials or meta-analyses. The 2014 Dusunen Adam case report (1) served precisely this purpose by alerting our multidisciplinary team to a plausible adverse drug reaction during a period of diagnostic uncertainty.
2. Clozapine's pharmacology should not be oversimplified or assumed to be uniformly protective against mood elevation. In patients who develop new-onset increased energy, decreased need for sleep, grandiosity, pressured thoughts, or increased goal-directed activity during clozapine initiation or re-initiation, medication-associated hypomania should be considered in the differential diagnosis after substance-induced, toxic-metabolic, neurological, and primary mood-disorder explanations have been reasonably assessed.
3. Management may differ from that of a first manic episode unrelated to medication exposure. Depending on the clinical context, options may include closer monitoring, dose adjustment, continued titration, augmentation with a mood stabilizer, or discontinuation of the suspected agent.

We therefore encourage colleagues worldwide to continue submitting well-documented reports of rare adverse effects associated with clozapine and other treatments. Such reports may not provide evidence of statistical association, but they can nevertheless inform clinical reasoning when similar cases are encountered.

We again thank the Editorial Board for maintaining an accessible archive that enabled our team to identify the 2014 report at a moment of clinical uncertainty. We hope that our own contribution (2) may, in turn, assist another team confronted with a similar diagnostic dilemma and promote the vigilant and reflective use of clozapine, which remains an essential treatment for treatment-resistant schizophrenia.

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LETTER TO THE EDITOR

Unexpected fluctuation in serum lithium concentrations during severe mania despite directly observed treatment

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Dear Editor,

Lithium's narrow therapeutic index necessitates close monitoring of serum concentrations. Subtherapeutic levels are usually attributed to non-adherence, inadequate dosing, sampling time, altered renal clearance, or drug interactions (1). Less familiar are unexplained fluctuations occurring during severe mania despite directly observed treatment.

A 20-year-old woman with bipolar disorder and two previous admissions for mania presented with a one-week history of insomnia, pressured speech, aggression, racing thoughts, and excessive spending. Examination revealed elevated mood, marked psychomotor agitation, and erotomanic and persecutory delusions; her Young Mania Rating Scale (YMRS) score was 23. She had no renal, hepatic, cardiac, or thyroid disease and reported no alcohol or substance use. She had previously taken lithium 900 mg/day for six months, which had been reduced to 600 mg/day because of tremor without toxicity. She had discontinued all medication six months before admission; Table 1 therefore reflects titration from zero. Thyroid function was normal on admission (thyroid-stimulating hormone [TSH] 0.83 mIU/L; free thyroxine [fT4] 0.93 ng/dL), and the pregnancy test was negative. By week 4, TSH had risen to 5.2 mIU/L

and fT4 had fallen to 0.76 ng/dL; these changes were monitored as possible early lithium-associated thyroid dysfunction.

The course is summarized in Table 1. All lithium measurements were obtained 12 hours after the last dose, at least five days after a dose change, and analyzed in the same laboratory; they therefore reflect steady-state trough concentrations. As the dose increased from 600 to 1200 mg/day, the serum concentration rose from 0.49 to 0.85 mEq/L, yet the concentration-to-dose (C/D) ratio declined progressively (0.82, 0.72, and 0.71). In week 4, despite an unchanged dose, the concentration fell to 0.38 mEq/L as the YMRS score rose to 36 (C/D ratio 0.32). Two samples obtained that day yielded concentrations of 0.40 and 0.38 mEq/L, indicating that the finding was not based on a single measurement. Medication administration under direct observation was confirmed, and a repeat sample three days later, with the dose unchanged, showed a concentration of 0.68 mEq/L (C/D ratio 0.57). She consumed no caffeinated beverages at any point, and caffeine withdrawal would, in any case, be expected to increase rather than decrease medication concentrations (2). There was no vomiting, diarrhea, polyuria, or fever. Agitation subsided after week 6, the YMRS score fell to 16 by week 9, and she was discharged in week 10.

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Table 1: Weekly course of lithium and valproate treatment, serum concentrations, lithium concentration-to-dose ratio, serum sodium, renal and hematological indices, Young Mania Rating Scale (YMRS) score, and treatment changes during admission

W	Lithium dose (mg/day)	Serum lithium (mEq/L)	C/D ratio (mEq/L)/(g/day)	Valproate dose (mg/day)	Serum valproate (µg/mL)	Sodium (mmol/L)	Creatinine (mg/dL)	eGFR* (g/dL)	Hb (g/dL)	YMRS	Treatment changes
1	600	0.49	0.82	–	–	141	0.78	111	13.1	23	Lithium 600 mg/day, olanzapine 5 mg/day, clonazepam 1 mg/day; quetiapine 25 mg added; lithium increased to 900 mg/day
2	900	0.65	0.72	–	–	137	0.73	121	13.6	25	Lithium increased to 1200 mg/day
3	1200	0.85	0.71	500	NM	138	0.62	131	12.9	NM	Olanzapine increased to 20 mg/day and quetiapine to 100 mg/day; valproate 500 mg/day initiated
4	1200	0.38 → 0.68 ^b	0.32 → 0.57 ^b	500 → 1000	31.5	140	0.68	128	13.3	36	Dose initially unchanged; regular medication intake confirmed under direct observation; lithium increased to 1500 mg/day at the end of the week
5	1500	0.80	0.53	1000	66.3	NM	NM	NM	NM	34	Clonazepam increased to 3 mg/day
6	1500	0.73	0.49	1000	84.5	141	0.72	123	12.7	38	Lithium increased to 1800 mg/day; propranolol added for tremor
7	1800	NM	–	1000	NM	139	0.78	111	12.9	20	Psychomotor agitation decreased; clonazepam reduced to 1 mg/day
8	1800 → 1500	1.21	0.67	1000 → 2000	78.4	139	0.83	103	12.3	20	Lithium reduced because of the elevated serum concentration; valproate increased to 2000 mg/day
9	1500	0.90	0.60	2000	92.5	138	0.75	117	12.7	16	Clonazepam discontinued
10	1500	1.02	0.68	2000	79.5	139	0.75	117	12.7	NM ^c	Patient discharged

W: Week; C/D: Concentration-to-dose ratio (serum lithium concentration in mEq/L divided by daily lithium dose in g); Hb: Hemoglobin; NM: Not measured. *eGFR is expressed in mL/min/1.73 m². All lithium measurements were obtained 12 hours after the last dose and at least five days after a dose change. ^bInitial measurement in week 4 and repeat measurement three days later, with the dose unchanged. ^cThe final YMRS assessment was performed in week 9 and was not repeated during the week of discharge.

Two points are noteworthy. First, estimated glomerular filtration rate (eGFR) increased from 111 mL/min/1.73 m² on admission to 131 mL/min/1.73 m² by week 3, while the C/D ratio declined from 0.82 to 0.71, which may reflect increased renal elimination. However, creatinine-based eGFR is only an indirect marker of true glomerular filtration rate (GFR) and lithium clearance, and lithium undergoes extensive tubular reabsorption; the change in eGFR therefore cannot quantitatively account for the decline. Hemoglobin remained between 12.3 and 13.6 g/dL, arguing against clinically meaningful hemodilution (3, 4). Second, the abrupt fall in week 4, when eGFR was unchanged, cannot readily be explained by renal function. At the height of the episode (weeks 4–6; YMRS 34–38), the mean C/D ratio was 0.45 when calculated using the initial week 4 value and 0.53 when using the repeat value, both lower than the mean of 0.65 during recovery (weeks 8–10), although this comparison depends on the interpretation of the 0.38 mEq/L result. Rittmannsberger and Malsiner-Walli (5) described comparable mood-dependent changes during stable dosing. One proposed explanation is redistribution of lithium into the intracellular compartment during acute mania; plasma and erythrocyte concentrations and their ratio have reportedly been associated with clinical state (6), although these were not assessed here. Valproate does not alter lithium pharmacokinetics in healthy volunteers (7), and olanzapine and quetiapine have no established effect on renal lithium clearance. Nevertheless, these concurrent changes preclude attributing clinical improvement to lithium alone.

Several limitations should be acknowledged. Fluid intake and urine output were not formally measured, and, without 24-hour urinary lithium excretion, renal clearance and tubular handling could not be assessed directly. No clinically apparent change in salt intake was recorded. Body weight increased from 64.3 to 80.2 kg, and its possible contribution to the observed changes could not be determined. Serum lithium concentrations reportedly vary across the menstrual cycle (8); the patient remained amenorrhoeic throughout, but because ovulation and gonadal hormone levels were not monitored, a hormonal contribution could not be assessed. Confirmation of the low concentration in two same-day samples reduces, but does not eliminate, the possibility of analytical error. Most importantly, the redistribution hypothesis was not tested directly: neither the erythrocyte-to-plasma lithium ratio (9) nor brain lithium concentration by ⁷Li magnetic resonance spectroscopy (10) was measured. Both would be valuable measures in future studies.

This case illustrates that serum lithium concentrations may fluctuate substantially during severe mania and that, under directly observed treatment, a single low concentration should not automatically be interpreted as evidence of non-adherence. Serial C/D ratios, interpreted alongside the clinical course and renal indices, may be more informative than isolated concentrations. Lithium doses escalated during an acute episode should also be reassessed during recovery to reduce the risk of subsequent toxicity (1).

Informed Consent: Written informed consent was obtained from the patient for the scientific use and publication of the patient information included in this case report.

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LETTER TO THE EDITOR

Phubbing as a social-cognitive failure: Affective theory of mind as a candidate mechanism

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Dear Editor,

Aksoy Avunduk et al. (1) provide a timely and methodologically careful examination of phubbing behavior in adolescents, demonstrating that social media addiction predicts phubbing both directly and through the sequential mediation of social anxiety and emotion regulation difficulties. Their serial mediation model advances our understanding of how digital behavioral patterns are embedded within broader profiles of emotional vulnerability during adolescence. We propose a complementary theoretical perspective that identifies a social-cognitive mechanism absent from the current model and that may account for some of the variance in phubbing behavior not explained by the pathways examined.

Phubbing, the act of ignoring a co-present social partner in favor of one's smartphone, is not merely a habitual behavior or a passive byproduct of social media addiction. At its core, phubbing implicates a sequence of social-cognitive operations that should be kept conceptually distinct: first, inferring that the co-present partner experiences being ignored and that their emotional state has changed as a result; and second, adjusting one's own behavior in light of that inference. Only the first of these belongs to affective theory of mind (ToM) proper, and it is this inferential process that we propose as a mechanism missing from the current model.

Terminological precision is essential to this argument, and we therefore use the following conceptual hierarchy throughout this Letter. Mentalization is the overarching capacity to understand one's own and others' behavior in terms of intentional mental states, such as beliefs, wishes, goals, and feelings, and is considered to be organized along several dimensions, including the cognitive-affective distinction (2). ToM denotes the component of this capacity directed toward representing other people's mental states and is conventionally divided into a cognitive component, involving the inference of others' beliefs, intentions, and goals, and an affective component, involving the inference of others' emotional states (3).

Accordingly, affective ToM is defined here narrowly as the inference and representation of another person's emotional mental state during interaction, without implying any broader construct. The regulation of one's subsequent behavior in response to such an inference, including accommodation to the social expectations prevailing in a given context, is a downstream social-regulatory process that is conceptually and empirically separable from the inferential capacity itself and is not part of the definition adopted here. Affective ToM is likewise distinct from empathy, which involves affective sharing of another person's emotional state rather than its representation.

Both cognitive and affective ToM continue to develop during adolescence, with a discernible

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developmental shift in middle adolescence and distinct neuropsychological correlates for each component (4), making the adolescent sample examined by Aksoy Avunduk et al. (1) particularly informative in this context. The mechanism we propose is therefore specific and testable: adolescents who engage in phubbing more frequently may be less accurate or less flexible in inferring the emotional states that their behavior elicits in co-present partners, independently of whether they subsequently adjust their behavior in light of those inferences.

Empirical work has begun to link social-cognitive capacity to digital social behavior in adolescents and young adults. Reduced empathic and mentalizing capacities have been associated with problematic smartphone use and phubbing, with lower empathy predicting greater phubbing in dyadic relationships (5). However, this evidence base has primarily examined empathy and broader mentalizing capacity rather than affective ToM in the narrow sense adopted here, and these constructs should not be treated as equivalent. Our proposal should therefore be regarded as a hypothesis about affective ToM that is rendered plausible by the available evidence rather than one that has already been established. The absence of a performance-based measure of affective ToM in the present study leaves this question open.

Qualitative evidence lends further support to a social-cognitive interpretation of phubbing. A recent scoping review of qualitative and mixed-methods studies synthesizes accounts in which co-present smartphone use disrupted face-to-face communication and attention to the immediate social environment. Difficulty maintaining eye contact and following the thread of a conversation emerged as characteristic features, while social norms and contextual factors substantially influenced whether a given instance of smartphone use was perceived as phubbing (6).

Both observations bear directly on the present argument. Disruption of eye contact and conversational tracking reduces access to the perceptual information, including facial expression, gaze, and prosody, that contributes to affective ToM in live interaction. The context dependence of phubbing further indicates that the phenomenon cannot be adequately captured simply as a fixed quantity of screen time. Recognizing that smartphone use is inappropriate in a particular context or distressing to a particular partner may itself require inference about that person's mental state. Taken together, these

observations support moving beyond a primarily addictive or habitual account of phubbing toward understanding it as an interpersonal phenomenon with a social-cognitive substrate.

The study's findings are also consistent with this hypothesis. Social anxiety, one of the mediators identified in the study, is associated with distortions in the interpretation of social evaluation: socially anxious individuals may be hypervigilant to cues of negative appraisal and may attribute hostile or critical intent to ambiguous social signals (7). This reflects a distortion of affective ToM rather than its simple absence, characterized by biased rather than deficient inference about others' emotional states.

Whether phubbing among socially anxious adolescents reflects active avoidance of situations that place substantial demands on affective ToM, such as face-to-face interactions requiring continuous inference about a partner's emotional state, or a failure to accurately represent the interpersonal consequences of smartphone-directed disengagement remains unclear. The current design cannot distinguish between these possibilities, but they have potentially different implications for intervention. Importantly, these two mechanisms are not mutually exclusive, and each provides an independent rationale for considering social-cognitive processes, albeit through different therapeutic targets.

To the extent that phubbing is associated with biased inference about others' emotional states, interventions might target these interpretive biases. To the extent that it reflects avoidance of social-cognitive demands, interventions might instead focus on strengthening social-cognitive skills and tolerance for real-time interpersonal interaction. Viewed as complementary rather than competing pathways, these possibilities suggest that emotion regulation training alone may not address all relevant mechanisms and that social-cognitive interventions targeting the recognition and interpretation of others' emotional states during interaction may provide an additional therapeutic target (8).

A second consideration concerns the bidirectional relationship between phubbing and affective ToM. Aksoy Avunduk et al. (1) acknowledge the cross-sectional nature of their design and appropriately refrain from making causal claims; we therefore raise this issue not as an oversight but as a promising direction for future research. Research on screen-based social interaction suggests that chronic reliance

on text- and image-mediated communication rather than face-to-face interaction may affect the development and maintenance of social-cognitive capacities that depend on the real-time processing of facial expressions, prosody, and bodily cues (9). If so, phubbing may not only reflect pre-existing social-cognitive vulnerabilities but could also contribute to their maintenance across adolescence, a developmental period during which affective ToM continues to mature (4).

Longitudinal studies would be well suited to test whether phubbing frequency at one time point predicts subsequent affective ToM performance after accounting for social anxiety and emotion regulation difficulties. Such studies should combine self-report measures of digital behavior with validated performance-based measures of affective ToM. The Reading the Mind in the Eyes Test (RMET), which requires participants to infer complex emotional and mental states from photographs of the eye region, is a widely used and readily implementable measure relevant to the affective ToM construct discussed here (10).

Aksoy Avunduk et al. (1) have produced a valuable and practically relevant study. The social-cognitive perspective outlined here suggests that affective ToM, which was not assessed in the current study, may represent an additional mechanism underlying the relationships among social anxiety, emotion regulation difficulties, and phubbing, as well as a potential target for intervention in adolescents who engage in problematic phubbing. Incorporating a brief, validated, performance-based measure of affective ToM, such as the RMET, into future studies of phubbing and digital behavior would substantially strengthen the mechanistic understanding of this growing clinical problem.

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LETTER TO THE EDITOR

Beyond the diagnosis of conduct disorder: The need for clinical formulation in justice-involved adolescents

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Dear Editor,

Justice-involved adolescents occupy a clinically and socially important position at the intersection of child and adolescent psychiatry and forensic psychiatry. Conduct disorder, attention-deficit/hyperactivity disorder (ADHD), depression, trauma-related symptoms, and substance use problems are common in this population (1). However, interpreting these findings solely within a narrow conduct disorder framework may be clinically limiting. Externalizing behavior can reflect the combined influence of developmental, traumatic, neurodevelopmental, and psychosocial factors. The specific gap addressed here is therefore not an absence of guidance on these domains, but a gap in their integration into routine practice. In child and adolescent forensic psychiatry, assessment may remain offense-centered, with relevant developmental and psychosocial information recorded as parallel diagnoses or risk factors rather than synthesized into a child-centered clinical formulation. The distinction we emphasize is between multidimensional assessment and clinical formulation: the former identifies relevant domains, whereas the latter explains how they interact in the individual case and translates them into prioritized, modifiable intervention targets. Accordingly, this

Letter focuses on how established trauma-informed, neurodevelopmental, educational, and psychosocial principles can be integrated into a concise, action-oriented clinical formulation to guide intervention.

A diagnosis of conduct disorder, by itself, does not explain why offending behavior began, why it persists, or which intervention is most likely to reduce future risk. When conduct problems are assessed, developmental level, learning capacity, emotional maturity, comorbid mental health difficulties, and the adolescent's educational and social care needs should be considered together (1–3). Similar externalizing behaviors may arise through different developmental and psychosocial pathways, including ADHD-related impulsivity, learning difficulties, trauma-related hyperarousal, substance use, adverse peer dynamics, family violence, school disengagement, and social disadvantage (1, 2, 4–6). When these pathways are not incorporated into a clinical formulation, diagnosis may become a static label rather than a clinically useful guide to intervention.

Trauma-informed approaches offer an important perspective in this context. Adverse childhood experiences are prevalent among justice-involved youth and have been associated with recidivism risk; however, this relationship should be understood as probabilistic rather than deterministic (4). Trauma-

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informed practice does not excuse harmful behavior. Rather, it seeks to understand how such experiences may affect emotion regulation, threat perception, attachment security, and problem-solving skills. At the same time, the evidence base for trauma-informed interventions remains limited, and findings should be interpreted cautiously given the heterogeneity of study designs (5). Attributing every harmful behavior to trauma may obscure individual agency and developmentally appropriate accountability. Trauma-informed care should therefore be embedded within a balanced formulation that also recognizes the individual and social consequences of behavior.

Neurodevelopmental and educational factors also require careful assessment. ADHD, intellectual disability, specific learning disorders, speech and language difficulties, traumatic brain injury, and fetal alcohol spectrum disorder are overrepresented in youth justice settings and may affect an adolescent's ability to understand legal processes, regulate behavior, or respond to standard interventions (2). School disengagement may reduce exposure to a structured and protective environment, while substance use may exacerbate impulsivity, susceptibility to peer influence, emotional dysregulation, and poor treatment adherence (6). These factors do not directly determine offending behavior, but they shape its clinical meaning and may help identify modifiable intervention targets.

This multidimensional perspective can be translated into practice through a brief, structured, and feasible assessment framework. Such an assessment should include urgent and modifiable domains, such as suicide risk, trauma-related symptoms, substance-related harms, untreated ADHD, learning needs, school exclusion or disengagement, family violence, and protective factors. Brief screening instruments may complement the clinical interview, provided that their validity, cultural appropriateness, and feasibility in forensic settings are carefully evaluated. Multidimensional assessment, however, is not equivalent to clinical formulation. A checklist can establish the presence of trauma exposure, ADHD, substance use, school disengagement, and family adversity; formulation asks how these factors interact in a particular adolescent and which should alter management. To make this formulation clinically usable, the 5P model can organize findings into presenting factors (the index behavior and current risks), predisposing factors (neurodevelopmental vulnerabilities, trauma history, and learning difficulties), precipitating factors (recent stressors, intoxication, or peer conflict), perpetuating

factors (untreated symptoms, ongoing substance use, school disengagement, or family instability), and protective factors (supportive relationships, school attachment, treatment engagement, and personal strengths). The 5P model is not proposed here as a novel framework; rather, its value in this context lies in converting established assessment domains into an explanatory and intervention-oriented synthesis. For example, in an adolescent with ADHD and conduct disorder, a 5P formulation identifying peer victimization as a precipitating factor and school disengagement as a perpetuating factor may shift management from diagnosis-focused treatment alone toward coordinated psychiatric care, school reintegration, family intervention, and cross-sector risk management. Each domain should be considered at both individual and environmental levels. The formulation should then conclude with a small number of prioritized, modifiable targets, such as immediate risk management, treatment of comorbid conditions, educational assessment, family intervention, or substance use treatment, so that it functions as an intervention map rather than a descriptive list.

This approach is also consistent with the principles underlying diversion programs. When appropriately structured, diversion can connect young people with mental health services, substance use treatment, educational support, family interventions, restorative practices, and social protection mechanisms. Such pathways may reduce unnecessary exposure to formal judicial proceedings while supporting public safety (7, 8).

The Turkish context makes this formulation perspective particularly timely. Recent child-centered justice initiatives in Türkiye emphasize protective and restorative approaches, community-based measures, and stronger intersectoral coordination for children in judicial processes (9). The Child Justice Center model also aims to conduct child-related judicial procedures in child-friendly settings and integrate judicial, psychosocial, educational, health, and social service responses (10). These reforms create a context in which clinical formulation can serve as an operational bridge between psychiatric assessment and justice, educational, health, and welfare pathways. Its practical contribution is not to introduce another assessment domain, but to provide a common clinical logic for translating psychiatric findings into coordinated decisions across these sectors. In this sense, the approach proposed here is not a new trauma-informed or neurodevelopmental framework, but a concise method for integrating established domains into a

child-centered, intervention-oriented formulation. In Türkiye, such a formulation could inform treatment priorities, psychiatric referrals, and recommendations for health, counseling, or educational measures. However, the proposed 5P-based approach remains a pragmatic framework whose impact on clinical or justice outcomes has not yet been empirically established.

In conclusion, the central issue is not whether justice-involved adolescents should receive trauma-informed, neurodevelopmentally sensitive, and multidisciplinary assessment; these principles are already well established. The more specific challenge is ensuring that such information does not remain a collection of diagnoses and risk factors organized around the offense. A child-centered clinical formulation should integrate these findings into an explanatory account of the adolescent's behavior and translate that account into a limited number of prioritized, modifiable intervention targets. In this sense, moving beyond conduct disorder means moving from diagnostic description toward clinically actionable formulation while preserving developmentally appropriate accountability.

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study clearly and objectively. Primary outcomes should be summarized in the text and supported by appropriately designed tables, figures, or graphs where applicable. The Discussion section should interpret and contextualize the findings in relation to previous studies, highlighting both supporting and conflicting evidence. Authors should discuss the implications of the findings, possible explanations for discrepancies, and the strengths and limitations of the study. The Conclusion section should provide a concise summary of the main results, their clinical or scientific relevance, and potential directions for future research. It should clearly state the key takeaway message derived from the study.

4.3.3.3. References

References should be numbered in parentheses and listed in the order in which they appear in the text, under the heading "References" at the end of the manuscript. The reference style must follow the Vancouver format.

There should be no inconsistency between the numbering and the reference order. Authors are solely responsible for ensuring the accuracy and completeness of all references. When there are seven or more authors, list the first six followed by "et al."

Abbreviations of journal names must comply with Medline/PubMed standards. Journals that are not indexed in Medline/PubMed should be written in full. Authors are encouraged to review previously published articles in the journal to ensure proper formatting and consistency when preparing the reference list.

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Tables, graphics, and figures should be numbered consecutively in Arabic numerals (e.g., Table 1, Figure 1) according to the order in which they are cited in the text. Their approximate placement should be clearly indicated within the manuscript.

Tables should present information concisely and effectively, allowing data to be displayed with clarity and precision. Presenting data in tables rather than in the text often reduces the overall manuscript length. Each table must appear on a separate page with a descriptive title. Column or row headings should be short and specific, and any explanatory notes should be placed as footnotes—not within the heading. All nonstandard abbreviations and statistical measures of variation (e.g., standard deviation, standard error) should be defined in footnotes. Line spacing for tables should be double-spaced, and the maximum allowable size is 120 characters in width and 70 lines in length.

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All figures should be submitted as separate high-quality digital files in JPEG format through the online submission system, in addition to being included at the end of the main document with their corresponding legends. Electronic images (e.g., photographs, radiographs, CT scans) must have a minimum resolution of 300 dpi to ensure print quality.

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This form must clearly specify the individual contributions of each author according to the ICMJE criteria. Each author should have participated in the conception, design, data acquisition, analysis, and/or interpretation, as well as in drafting or revising the manuscript and approving its final version. Authors who do not meet all authorship criteria should be listed in the acknowledgments section.

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Research articles present substantial and original scientific findings within the scope of the journal. Each research article should contain an abstract, keywords, introduction, methods, results, discussion, conclusion, references, and tables or figures. The abstract and main text must follow the structured format described above. Ethics committee approval and informed consent information must be obtained and clearly stated in the manuscript.

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Table: Manuscript types and corresponding word, abstract, reference, and table/figure

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table/ figure limit (total)
Research article	3500	250 (<i>structured</i>)	50	6
Systematic reviews and meta-analyses	4000	250	No limit	10
Brief report	1500	250 (<i>structured</i>)	15	2
Letter to the editor	750	No abstract	10	1
Guest editorial	1200	No abstract	20	2

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