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Τριμηνιαία έκδοση
της Ελληνικής Ψυχιατρικής Εταιρείας
Διονυσίου Εγγίνου 17, 115 28 Αθήνα
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Manuscripts should be submitted for publication through the above website or should be sent as an attachment by email to editor@psychiatriki-journal.gr

PSYCHIATRIKI

Quarterly journal published
by the Hellenic Psychiatric Association
17, Dionisiou Eginou str., 115 28 Athens
Tel.: +30-210-77 58 410, Fax: +30-210-77 09 044

Publisher:
Hellenic Psychiatric Association
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Annual subscriptions of the Journal:

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PSYCHIATRIKI

Quarterly journal published by the Hellenic Psychiatric Association

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Editorial

Artificial Intelligence in psychotherapy: Inevitable evil or developmental evolution? Complementation or parallel universe?

ARTICLE HISTORY: Received 29 October 2025/Published Online 20 December 2025

“This is an artificial intelligence chatbot and not a real person. Treat everything it says as fiction. What is said should not be considered facts or advice,” these are the first words that Gharacter.Ai, a counseling chatbot, says to those who turn to it for help.

Is it common for humans to turn to machines for psychotherapy? We do it for most of our daily lives, often taking it for granted. In fact, we often prefer to interact with algorithms rather than other homo sapiens. Is it just as easy or efficient to seek help from machines for mental health issues? The global market for chatbots for mental health and therapy was worth \$1.37 billion in 2024 and is expected to reach approximately \$2.38 billion by 2034, growing at a compound annual growth rate (CAGR) of 5.7% from 2024 to 2034.¹ Griefbots, AI machines that help our deceased relatives continue their “presence” with us, are also on the rise.²

What are the characteristics of chatbots that are becoming increasingly sought after? They are immediately accessible at any time 24 hours a day, synthesize all human knowledge on the subject in the optimal combination, are fully accepting and non-judgmental, and are designed to ally with the user and keep them in touch. And they are clearly cheaper.³ The increasing demand for psychotherapy, in contrast to the reduced availability of therapists (especially in the public sector), implies long waits and worsening of symptoms.⁴ The existence of “therapists” who are ready at any time, do not get tired, and can listen and encourage, sounds like a promising solution.⁵ What does it matter if they are not human? For some, this is still a guarantee of independence, objectivity, and protection from the adverse effects of the therapeutic relationship (dependence, guidance, eroticization, aggression). How effectively can a chatbot play the role of a therapist? Can it keep the conversation interesting, but can it keep the boundaries? Can it understand when the conversation is getting off track? AI tries to keep the user engaged, just as our algorithm suggests something that appeals to us on social media.⁶ Is this therapeutic?

Can the absence of human contact and closeness be compensated for? Some patients struggle with this very component of psychotherapy, human interaction. Chatbots are based on the most likely linguistic sequence. Can they manage and recognize emotions? However, AI's ability to recognize emotions and facial expressions is constantly improving.⁷ AI is already better than humans in verbal and non-verbal tests and has conquered areas where it was inferior just a few years ago (it has won the strategy game Go, and it recognizes more cats in photos).⁷ Regarding psychotherapy, there are controlled studies from Japan, Australia, Europe, and the USA that show good therapeutic results in specific conditions (depression, obsessive-compulsive disorder) with AI therapy alone or in a hybrid model^{8–10} or in issues related to psycho-education.⁵ However, there are also reports of worsening suicidality.¹¹

But what are the characteristics of a non-human therapeutic relationship? Is there empathy? What does a chatbot mean when it says, “I understand you”? What does a human therapist mean when they say, “I understand you”? How does a human feel when talking to a non-human? Is there transference? What kind of transference is it?¹² If transference to a human therapist is towards the other, transference to an AI therapist will be towards the big Other? If transference is inherent in the human interface, how will it be shaped for the next generation of people, who are growing up in a digital world from the ground up, touching their mobile phones more than other people?

But when we talk about a chatbot, are we talking about a therapist or a tool?¹³ How is it different from an MRI scanner? Is our relationship competitive, or can it be used as a tool? Can AI be trained and respond to requests, as a specific therapist would respond and be his assistant? (If we consider that it can be trained and write like Shakespeare, the answer is probably yes).

Are there ethical issues? An AI therapy has the biases of the database on which it is based (what biases do human therapists have?). Ethics, however, follow the changes in society; they do not shape them. There are already AI influencers with thousands of followers, AI actors with their own fans, and AI artistic works that are not easily (or at all) distinguishable from human ones. What if they do not contain a “soul deposit” like the latter?

Is AI therapy safe? Is there a privacy issue like human therapists? It is unlikely (for now) that two therapeutic chatbots will gossip about their patients, but we all know what data leaks and cyberattacks on computer networks mean.

I started writing this text to highlight the disadvantages of AI therapy compared to the psychotherapy we learned in the 20th century. As I wrote, one by one, the disadvantages seemed not to be much different from those that appear in traditional psychotherapy. The only argument that remains is that the things that are exchanged between people are more complete, stronger, and more permanent. Not because the therapy is perfect (quite the opposite), but because they also occur at a level of unspoken, emotional interaction. At this stage, AI therapy has obvious flaws. In the future, it may be perfected, but again, a human “good enough therapist” may be better for us.

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Άρθρο σύνταξης

Η Τεχνητή Νοημοσύνη στην ψυχοθεραπεία: Αναπόφευκτο κακό ή αναπτυξιακή εξέλιξη; Σύμπλευση ή παράλληλο σύμπαν;

ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 29 Οκτωβρίου 2025/Δημοσιεύθηκε Διαδικτυακά 20 Δεκεμβρίου 2025

«Αυτό είναι ένα chatbot τεχνητής νοημοσύνης (AI) και όχι ένα πραγματικό πρόσωπο. Αντιμετωπίστε όλα όσα λέει ως μυθοπλασία. Αυτά που λέγονται δεν πρέπει να θεωρούνται γεγονότα ή συμβουλές», αυτά είναι τα πρώτα λόγια που το Gharacter.AI ένα chatbot συμβουλευτικής, λέει σε αυτούς που απευθύνονται σε εκείνο για βοήθεια.

Είναι συχνό οι άνθρωποι να απευθυνόμαστε σε μηχανές για ψυχοθεραπεία; Το κάνουμε, άλλωστε για τα περισσότερα στοιχεία που απαρτίζουν την καθημερινότητά μας, πολλές φορές θεωρώντας το αυτονόητο. Αρκετές φορές μάλιστα, προτιμούμε την επαφή μας με αλγορίθμους παρά με άλλους homo sapiens. Είναι το ίδιο εύκολο ή αποδοτικό να αναζητούμε βοήθεια από μηχανές σε θέματα ψυχικής υγείας; Το μέγεθος της παγκόσμιας αγοράς chatbots για την ψυχική υγεία και τη θεραπεία αντιπροσώπευε 1,37 δισεκατομμύρια δολάρια ΗΠΑ το 2024 και αναμένεται να φτάσει περίπου τα 2,38 δισεκατομμύρια δολάρια ΗΠΑ έως το 2034, αυξανόμενο με σύνθετο ρυθμό ανάπτυξης (CAGR) 5,7% από το 2024 έως το 2034.¹ Αυξανόμενη είναι και η χρήση των griefbots, μηχανών τεχνητής νοημοσύνης (AI) που βοηθούν να συνεχίσουν οι νεκροί μας την «παρουσία» τους μαζί μας.²

Ποια είναι τα χαρακτηριστικά που έχουν τα chatbots και γίνονται όλο και πιο περιζήτητα; Είναι άμεσα προσβάσιμα ανά πάσα στιγμή όλο το 24ωρο, συνθέτουν όλη την ανθρώπινη γνώση γύρω από το θέμα με τον βέλτιστο συνδυασμό, αποδέχονται πλήρως και δεν κρίνουν, και είναι φτιαγμένα να συμμαχούν με τον χρήστη και να τον διατηρούν σε επαφή. Και σαφώς είναι φθηνότερα.³ Η όλο και μεγαλύτερη ζήτηση για ψυχοθεραπεία, σε αντιδιαστολή με τη μειωμένη δυνατότητα για θεραπευτές (ειδικά στον δημόσιο τομέα) συνεπάγεται μεγάλες αναμονές και επιδείνωση των συμπτωμάτων.⁴ Η ύπαρξη «θεραπευτών» που βρίσκονται έτοιμοι ανά πάσα στιγμή, δεν κουράζονται, και μπορούν να ακούνε και να ενθαρρύνουν, ακούγεται σαν μια πολλά υποσχόμενη λύση.⁵ Τι πειράζει κι αν δεν είναι άνθρωποι; Ίσα-ίσα, αυτό για κάποιους αποτελεί εχέγγυο ανεξαρτησίας, αντικειμενικότητας και προφύλαξης από τις ανεπιθύμητες ενέργειες της θεραπευτικής σχέσης (εξάρτηση, καθοδήγηση, ερωτικοποίηση, επιθετικότητα). Πόσο καλά μπορεί ένα chatbot να παίξει τον ρόλο του θεραπευτή; Μπορεί να κρατήσει το ενδιαφέρον, αλλά μπορεί να κρατήσει τα όρια; Μπορεί να καταλάβει πότε η συζήτηση εκτροχιάζεται; Η AI προσπαθεί να κρατήσει τον χρήστη στη συζήτηση, όπως και ο αλγόριθμος μας προτείνει κάτι που μας ελκύει στα social media.⁶ Είναι αυτό θεραπευτικό;

Η απουσία της ανθρώπινης επαφής και εγγύτητας μπορούν να αναπληρωθούν; Υπάρχουν ασθενείς που δυσκολεύονται με αυτό ακριβώς το συστατικό μιας ψυχοθεραπείας, την ανθρώπινη αλληλεπίδραση. Τα chatbots βασίζονται στην πιθανότερη γλωσσική αλληλουχία, μπορούν, όμως, να διαχειριστούν και να αναγνωρίσουν συναισθήματα; Η δυνατότητα της AI να αναγνωρίζει συναισθήματα και εκφράσεις του προσώπου βελτιώνεται συνεχώς.⁷ Η AI είναι ήδη καλύτερη από τον άνθρωπο σε δοκιμασίες που δεν βασίζονται στον λόγο και έχει κατακτήσει πεδία στα οποία ήταν υποδεέστερη μόλις λίγα χρόνια πριν (έχει νικήσει στο παιχνίδι στρατηγικής γκο, αναγνωρίζει περισσότερες γάτες σε φωτογραφίες, κ.ά.)⁶ Όσον αφορά στην ψυχοθεραπεία, υπάρχουν ελεγχόμενες μελέτες από την Ιαπωνία, Αυστραλία, Ευρώπη και ΗΠΑ που δείχνουν καλά θεραπευτικά αποτελέσματα σε συγκεκριμένες καταστάσεις (κατάθλιψη, ιδεοψυχαναγκαστική διαταραχή) με τη θεραπεία AI, μόνη ή σε υβριδικό μοντέλο⁸⁻¹⁰ ή σε ζητήματα που αφορούν στην ψυχο-εκπαίδευση.⁵ Υπάρχουν αντίθετα, και αναφορές για επιδείνωση της αυτοκτονικότητας.¹¹

Ποια είναι, όμως, τα χαρακτηριστικά μιας μη ανθρώπινης θεραπευτικής σχέσης; Υπάρχει ενσυναίσθηση; Τι εννοεί ένα chatbot όταν λέει «σε καταλαβαίνω»; Τι εννοεί ένας άνθρωπος-θεραπευτής όταν λέει «σε καταλαβαίνω»; Πώς νιώθει ένας άνθρωπος όταν μιλά σε μη άνθρωπο; Υπάρχει μεταβίβαση; Τι είδους είναι αυτή;¹² Αν η μεταβίβαση σε έναν άνθρωπο θεραπευτή είναι απέναντι στον άλλον, η μεταβίβαση σε έναν AI θεραπευτή θα είναι απέναντι στον μεγάλο Άλλον; Αν η μεταβίβαση είναι ίδιον της ανθρώπινης διεπαφής, πώς αυτή θα διαμορφωθεί για τους ανθρώπους της επόμενης γενιάς, που αναπτύσσονται εξ αρχής σε έναν ψηφιακό κόσμο, αγγίζοντας περισσότερο το κινητό τους τηλέφωνο, παρά άλλους ανθρώπους;

Όταν, όμως, μιλάμε για ένα chatbot, μιλάμε για έναν θεραπευτή ή για ένα εργαλείο;¹³ Σε τι διαφέρει από ένα μαγνητικό τομογράφο; Είναι η σχέση μας ανταγωνιστική ή μπορεί να χρησιμοποιηθεί σαν εργαλείο; Μπορεί η AI να εκπαιδευτεί και να απαντά στα αιτήματα, όπως θα απαντούσε ένας συγκεκριμένος θεραπευτής και να είναι ο βοηθός του; (αν σκεφτούμε ότι μπορεί να εκπαιδευτεί και να γράφει σαν τον Σαίξπηρ, η απάντηση είναι μάλλον καταφατική).

Υπάρχουν ηθικά ζητήματα; Μία AI θεραπεία έχει τις προκαταλήψεις που έχει η βάση δεδομένων στην οποία βασίζεται (οι άνθρωποι θεραπευτές ποιες προκαταλήψεις έχουμε); Η ηθική, όμως, ακολουθεί τις αλλαγές σε μια κοινωνία, δεν τις διαμορφώνει. Υπάρχουν, ήδη, AI influencers με χιλιάδες ακολούθους, AI ηθοποιοί με δικούς τους θαυμαστές και AI καλλιτεχνικά έργα που δεν ξεχωρίζουν εύκολα (ή και καθόλου) από τα ανθρώπινα. Τι κι αν δεν περιέχουν «κατάθεση ψυχής» όπως τα τελευταία.

Είναι ασφαλής η θεραπεία AI; Υπάρχει θέμα απορρήτου αντίστοιχο με τους ανθρώπους-θεραπευτές; Είναι απίθανο (προς το παρόν) δύο θεραπευτικά chatbots να κουτσομπολεύουν τους ασθενείς τους, αλλά όλοι γνωρίζουμε τι σημαίνει διαρροή στοιχείων και κυβερνο-επίθεση σε δίκτυα υπολογιστών.

Ξεκίνησα να γράφω αυτό το κείμενο με σκοπό να αναδείξω τα μειονεκτήματα της AI θεραπείας απέναντι στην ψυχοθεραπεία που μάθαμε τον 20ο αιώνα. Όσο έγγραφα, ένα-ένα τα μειονεκτήματα φαίνονταν να μη διαφέρουν ιδιαίτερα από αυτά που εμφανίζονται και στην παραδοσιακή ψυχοθεραπεία. Το μόνο επιχείρημα που μένει, είναι ότι τα πράγματα που διαμείβονται μεταξύ των ανθρώπων είναι πιο πλήρη, πιο δυνατά και πιο μόνιμα. Όχι γιατί η θεραπεία είναι τέλεια (το αντίθετο μάλιστα), αλλά γιατί συμβαίνουν και σε ένα επίπεδο άρρητης, συναισθηματικής αλληλεπίδρασης. Στην παρούσα φάση, η AI θεραπεία έχει εμφανείς ατέλειες. Στο μέλλον πιθανόν να τελειοποιηθεί, αλλά και πάλι, ίσως είναι καλύτερος για εμάς ένας ανθρώπινος «αρκετά καλός θεραπευτής».

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Research article

Exposure and response of private practice psychiatrists in Greece to illicit substance use-related treatment requests: A cross-sectional survey

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ARTICLE HISTORY: Received 13 March 2025/Revised 29 June 2025/Published Online 20 December 2025

ABSTRACT

The use of illicit substances is a major public health problem. While individuals with substance use problems primarily seek treatment in specialized treatment programs, the role, exposure, and response of private practice psychiatrists to requests for substance-related issues remain unclear. This study aims to assess private practice psychiatrists' exposure to and response to treatment requests for substance use-related problems, along with examining the requests' characteristics. A cross-sectional online anonymous survey was administered involving private practice psychiatrists in Greece between January and February 2024. A total of 100 private practice psychiatrists responded to the survey (response rate ~10%; 53.0% male, aged 49.5 (SD=9.3) years, with 13.7 (SD=9.9) years of professional experience, and 59.0% with a private office in the Attica/Athens region. Most participants (84.0%) reported exposure to requests for substance use treatment during the last 12 months, with 69.0% of them (58% of the total) accepting to offer treatment. The most frequently reported categories of substances included cannabis and cocaine/crack. High rates of comorbidity with problematic alcohol use, multiple substance use, and other mental disorders were also reported. Pharmacotherapy and cognitive behavioral therapy were the treatments most commonly used. Factors associated with accepting to offer treatment included past specialized training in addiction ($p<0.001$), past or current employment in treatment facilities ($p=0.002$), self-reported expertise in addictions ($p=0.017$), previous training during specialty in substance use departments ($p=0.001$), and use of motivational interviewing ($p=0.011$). Around 70% of participants who did not accept cases believed patients would be better treated in specialized substance use treatment programs. Among all participants, 63.6% were willing to accept future treatment requests—significantly higher percentage (93.1%) among those who had accepted similar requests before, compared to those who had not (19.2%, $p<0.001$). In conclusion, apart from specialized addiction services, a substantial number of private practice psychiatrists in Greece were also exposed to and accepted treatment requests for illicit substance use-related problems, with most frequently encountering requests related to cannabis and cocaine use. Future research should investigate the characteristics of patients treated for illicit substance use-related issues in private settings and the services provided to them.

KEYWORDS: Private practice psychiatrists, addiction, substance use disorders, treatment requests, perceptions.

Introduction

Illicit substance use disorders (ISUDs) are highly prevalent globally, with recent estimates indicating that 64 million individuals were affected worldwide in 2022, with only one in eleven receiving some form of treatment.¹ In Europe, the most used illicit substances in 2023 were cannabis (22.8 million users), cocaine (2.5 million users), MDMA (2.2 million users), amphetamines and methamphetamines (1.5 million users), and heroin and opioids (860,000 users). In 2022, treatment was provided to at least 92,000 cannabis users, 63,000 opioid users, 29,000 cocaine users, and 10,000 amphetamine users.²

In Greece, it is estimated that about 10,600 individuals use opioids.³ In 2022, approximately 3,500 individuals entered treatment in any one of the 167 specialized treatment/counseling centers operating in the country, with three-fourths of them (77.3%) reporting polydrug use. Opioids (mostly heroin) were the primary drug most frequently mentioned upon entry (46.7%), followed by cannabis (27.8%), cocaine/other stimulants (21.8%), and 'other substances' (3.8%).³ Finally, 34.3% of individuals on substance use-related treatment have also been diagnosed with an additional psychiatric disorder, with an increasing trend over the years.⁴

Despite the high prevalence of ISUDs, relatively few affected individuals seek treatment. Both health care system characteristics and individual factors serve as barriers to enrolling in specialized treatment services.^{5,6} Most studies identify stigma as the primary barrier to treatment, along with long waiting times, denial of the problem, living in rural areas, and lack of awareness of available treatment options.⁶⁻¹⁰ Furthermore, the female population is most affected, as it is often underrepresented in treatment programs.¹ Conversely, comorbid mental illnesses facilitate treatment seeking.¹¹⁻¹³

Specialized addiction treatment centers are well-studied for ISUD treatment. However, the role of private practice psychiatrists, particularly those working in office-based settings, remains under-researched. This is particularly relevant in Greece, where a notable proportion of psychiatrists work independently in private practice, underscoring the need to better understand their involvement in ISUD treatment requests. A previous study found that patients with SUDs and comorbid psychiatric disorders were more likely to seek treatment from psychiatrists than those with either disorder alone, often preferring psychiatrists with expertise in addiction.¹⁴ Another study examined 865 psychiatrists, classifying them into high-SUD providers (>51% cases with SUD) and non-high-SUD providers. High-SUD providers were typically younger and less likely to

practice privately (14.0% vs 55.4%), with mood disorders being the most common comorbidity among patients treated by them.¹⁵ A recent cross-sectional study in India reported that among 998 individuals with SUD, 14.4% initially sought treatment from private practice psychiatrists, 6.0% from private medical practitioners, while most first contacted public-funded addiction treatment services.¹⁶

In Greece, 6.8% of individuals entering public addiction treatment centers reported a health practitioner as their key point of referral.³ To our knowledge, no national studies have examined the exposure and response of private practice psychiatrists in Greece to treatment requests for ISUDs. Hence, the purpose of the present study is to examine the extent to which private practice psychiatrists in Greece encounter and accept treatment requests for illicit substance use-related issues and to investigate their treatment approaches and service characteristics.

Material and Method

Design

The study was an exploratory cross-sectional survey based on the online completion of a self-explanatory, anonymous questionnaire addressed to private practice psychiatrists in Greece in the period January-March 2024.

Participants

The target population consisted of all private practice adult psychiatrists actively practicing psychiatry in Greece. According to the Panhellenic Medical Association (2023), approximately 1800 licensed adult psychiatrists were registered nationwide. In Greece, adult psychiatry and child and adolescent psychiatry are distinct medical specialties with separate training and licensing; thus, this figure does not include child and adolescent psychiatrists. Inclusion criteria were: (a) completion of an adult psychiatry specialty and (b) actively practicing the profession. Exclusion criteria were (a) specialization in child & adolescent psychiatry and (b) being employed exclusively in the public service sector. The study employed a non-probabilistic sampling procedure: first, the survey was mailed to approximately 1500 psychiatrists, members of the Hellenic Psychiatric Association. It should be noted that not all licensed adult psychiatrists in Greece are members of this association, and a small number of child and adolescent psychiatrists may also be included in this figure. Next, the study was shared by the researcher in two Facebook groups of psychiatrists. Finally, personalized invitation emails were sent to 582 private practice psy-

chiatrists with publicly available online email or contact details.

Study setting

Data collection was performed online via the LimeSurvey platform, ensuring anonymity. The study was designed in accordance with the principles of the Helsinki Declaration (2013) and the provisions of Regulation (EU) 2016/679 on the protection of personal data and was ethically approved by the Medical Ethics Committee of the University Mental Health, Neurosciences, & Precision Medicine Research Institute (UMHRI, ΕΠΙΨΥ; Decision no: 2345-13/11/2023).

Measures/Tools

Due to the lack of existing instruments, a structured, self-explanatory questionnaire was developed ab initio and subsequently reviewed by a psychiatrist specializing in the field of addiction to ensure content relevance and clarity. Although a formal pilot study was not conducted due to time constraints, this expert review served to enhance the face validity of the tool.

The questionnaire was designed to take no more than 10 minutes to complete and consisted of 62 items across four sections: (a) sociodemographic and clinical practice characteristics (18 questions), (b) exposure to and acceptance of substance use-treatment requests (4 questions), (c) clinical characteristics and management of accepted cases (30 questions), and (d) psychiatrists' reasoning for case denial and intention for accepting future requests (10 questions). Participants' exposure was assessed across five categories of illicit substances: (a) cannabis/cannabinoids, (b) heroin/other opioids (including non-prescribed use or abuse of opioid substitutes or agonists), (c) cocaine, (d) other stimulants (e.g., methamphetamine, amphetamine), and (e) other illicit substances. The complete English version of the questionnaire used in this survey is openly available in the Open Science Framework at: https://osf.io/kfma9/?view_only=e2d06030a9194c2ea8381c6244ce73ac.

Statistical analysis

Standard descriptive analyses were first conducted for the whole sample as a preliminary. The Pearson chi-square test for independence (with Bonferroni post hoc correction where applicable) or Fisher's exact test was used to investigate significant differences in the ratio of two characteristics expressed with categorical data. The student's t-test for independent samples was conducted to examine whether the mean of a continuous variable differed significantly between the two levels of a categorical variable. A level of $\alpha=0.05$ was used to re-

ject the null hypothesis and determine the presence or absence of statistically significant differences (although differences at $\alpha=0.1$ were also presented as a trend). All analyses were performed in SPSS (IBM Corp. Released 2023. IBM SPSS Statistics for Windows, Version 29.0.2.0 Armonk, NY: IBM Corp).

Results

Participant characteristics

A total of 100 private practice psychiatrists returned a valid questionnaire, 53.0% males with a mean age of 49.5 (SD=9.3) years (age range 30–75). More than half (54.0%) practiced exclusively in the private sector, while the remaining 46.0% were also employed in the public sector. The majority (59.0%) operated their private practices within the Athens/Attica region (table 1).

In their vast majority (83.0%), psychiatrists reported assessing substance use history during initial appointments, while 17.0% identified themselves as specialists in managing substance use cases. Cognitive-behavioral therapy was the most frequently utilized psychotherapeutic intervention, reported by 60.6% of participants (table 2).

Exposure to and acceptance of SUD-related treatment requests

Most of the participants (84.0%) reported encountering at least one ISUD-related treatment request in the past (table 3). Ranked in order, treatment requests most involved cannabis (80.0%), cocaine (64.0%), heroin/other opioids (51.5%), other stimulants (40.0%), and other illicit substances (15.0%) (table 3).

Over half of the total sample (58.0%) accepted at least one treatment request. Acceptance rates were highest for cannabis (52.0% of the total sample) and cocaine (29.0% of the total sample) (table 3).

Prior exposure of psychiatrists to treatment requests for substance use was associated with having trained during their specialty at a substance use treatment unit ($p=0.003$), having received additional specialized training in addiction management beyond their specialty ($p=0.005$), and having current or past employment at a substance use treatment facility (vs never, $p=0.004$) (table 4).

Whether a private practice psychiatrist had previously accepted a treatment request for substance use appeared to be associated with having trained during their specialty at a substance use treatment unit ($p=0.001$), having specialized training in addiction management beyond specialty ($p<0.001$), having current or past employment with a substance use treatment facility (vs never, $p=0.002$), having specialized in SUD

Table 1. General characteristics of private practice psychiatrists (n=100).

	N (%)
Gender	
Male	53.0 (53)
Female	47.0 (47)
Age, years, Mean (SD)	49.5 (9.3)
Age groups	
30–34	3.0 (3)
35–39	11.0 (11)
40–44	14.0 (14)
45–49	25.0 (25)
50–54	23.0 (23)
55–59	11.0 (11)
60+	13.0 (13)
Country of medical degree acquisition	
Greece	83.0 (83)
Other	17.0 (17)
Educational level	
Bachelor's degree only	54.5 (54)
Master's degree	37.4 (37)
Doctoral degree	8.1 (8)
Country of medical specialty training	
Greece	90.9 (90)
Other	9.1 (9)
Training in a substance use treatment unit during a specialty	
Yes	63.6 (63)
No	36.4 (36)
Additional training in substance uses disorders beyond specialty	
Yes	44.4 (44)
No	55.6 (55)
	N (%)
Practice setting	
Exclusively private	54.0 (54)
Private and public/non-governmental organizations	46.0 (46)
Employment or collaboration with substance use treatment facilities	
Yes, currently	9.0 (9)
Yes, in the past	29.0 (29)
No, never	62.0 (62)
Years of practice as a private practice psychiatrist, years, mean (SD)	13.7 (9.9)
Private office location	
Attica (Athens)	59.0 (59)
Central Macedonia (Thessaloniki)	18.0 (18)
Other regions	23.0 (23)
Urbanicity of private office location	
Regional capital, city center	49.5 (49)
Regional capital, neighborhood near city center	18.2 (18)
Regional capital, city suburb	28.3 (28)
Other areas of the region	4.0 (4)

Table 2. Characteristics of the therapeutic/clinical approach of participants in the study (n=100).

	N (%)
Assessment of substance use history	
Yes, always	83.0 (83)
Depending on the clinical presentation	16.0 (16)
No	1.0 (1)
Self-reported specialization in substance uses disorder management	
Yes	17.0 (17)
No	83.0 (83)
Therapeutic approaches beyond pharmacological treatment*	
Cognitive-behavioral therapy	60.6 (57)
Psychodynamic psychotherapy or psychoanalysis	31.9 (30)
Motivational interviewing	30.9 (29)
Systemic therapy	17.0 (16)
Dialectical-behavioral therapy	4.3 (4)
Other therapeutic approaches (e.g., existential, Gestalt, etc)	7.4 (7)

*In general, regardless of the type of case

management ($p=0.017$), and additionally utilizing motivational interviewing ($p=0.011$) (table 4).

Reasons for declining SUD-related treatment requests

Nearly one-third (31.0%) of those who received treatment requests for ISUD declined to accept such cases. The majority cited the belief that these cases require management in specialized settings, with refusal rates ranging from 53.6% for other stimulants to 79.5% for heroin/opioids. Additional reasons for decline included insufficient training, lack of interest, and other factors (figure 1).

Intention to accept future ISUD-related treatment requests

Regardless of the substance involved or their prior experience, approximately two-thirds (63.6%) of the participants responded that they would accept the next ISUD-related treatment request. Cannabis was the most likely substance to be accepted (61.6%), followed by cocaine (31.3%), other substances (24.2%), other stimulants (16.2%), and heroin/opioids (13.4%). Regardless of the substance, psychiatrists who had previously accepted similar cases were significantly more likely (93.1%) to accept subsequent requests, compared to those without prior acceptance (19.2%, $p<0.001$). This difference remained statistically significant across all substance categories except for "other substances", where psychia-

Table 3. Characteristics of (a) exposure to and (b) management of treatment requests related to SUD, by private practice psychiatrists participating in the study, by substance type.

Substance Type	Exposed (for the entire sample, n=100)	Accepted (among those who were exposed)	Accepted (for the entire sample, n=100)
	% (N)	% (N)	% (N)
Any substance*	84.0 (84/100)	69.0 (58/84)	58.0 (58/100)
Cannabis/Cannabinoids	80.0 (80/100)	65.0 (52/80)	52.0 (52/100)
Cocaine/ Crack	64.0 (64/100)	45.3 (29/64)	29.0 (29/100)
Other stimulants	40.0 (40/100)	30.0 (12/40)	12.0 (12/100)
Heroin/Other opioids	51.5 (50/97)	22.0 (11/50)	11.0 (11/100)
Other substances	15.0 (15/100)	66.7 (10/15)	10.0 (10/100)

*Includes any of the categories: "cannabis/cannabinoids", "cocaine/crack", "other stimulants", "heroin/other opioids", or "other substances"

trists without prior experience were more likely (94.2%) to accept the next request compared to those with experience (63.6%, $p < 0.001$, although this finding should be viewed cautiously due to the small number of observations involved (table 5).

Characteristics of the SUD-related treatment cases

Participants were asked to estimate the percentage of ISUD cases that had previously sought treatment at public addiction treatment services. The response «in 0% of cases» was reported by 21.8% of psychiatrists for cannabis, 11.1% for cocaine, 27.3% for 'other stimulants', and 9.1% for heroin/opioids (not shown in Table). The most frequent response, «in 10% of cases,» was reported by 42.3% of psychiatrists for cannabis cases, 29.6% for cocaine, 36.4% for 'other stimulants', while the response «in at least 50% of cases» was reported by 72.7% of psychiatrists regarding heroin/opioids.

Participants were also asked about their treatment approaches for accepted ISUD cases. Pharmacotherapy was reported by 92.3% of the respondents for cannabis cases, 93.1% for cocaine, 91.7% for other stimulants, and 81.8% for heroin/opioids. Among psychosocial interventions, CBT (50% for cannabis, 62.1% for cocaine, 41.7% for other stimulants, 54.5% for heroin/opioids) and motivational interviewing (28.8% for cannabis, 27.6% for cocaine, 27.6% for other stimulants, 27.3% for heroin/opioids) were most frequently reported.

Furthermore, regarding concurrent alcohol abuse in cannabis cases, most psychiatrists (34.6%) reported «in 20% of cases», while 32.7% reported polysubstance use «in at least 50% of cases». For cocaine, 79.3% reported alcohol abuse and polysubstance use in at least 50% of cases. For "other stimulants", 58.3% reported alcohol

abuse and 66.0% polysubstance use «in at least 50% of cases». For heroin/opioids, 36.4% reported alcohol abuse in 20% of cases, while 81.8% noted polysubstance use «in at least 50% of cases.

Furthermore, participants were asked to estimate the comorbidity rate between ISUDs and other mental health disorders in cases accepted. The response «in at least 50% of cases» was reported by 62.7% of the participants for cannabis cases, 69.0% for cocaine, 75% for 'other stimulants', and 36.4% for heroin/opioids cases. Mood disorders were reported by 78.4% of the participants for cannabis cases, 82.8% for cocaine, 50% for 'other stimulants', and 45.5% for heroin/opioids. Personality disorders were reported by 81.8% for heroin/opioids, 69% for cocaine, 52.9% for cannabis, and 50% for other stimulants.

Discussion

Historically, the number of individuals with ISUDs who seek and ultimately receive treatment at addiction treatment centers has been considerably lower compared to the total number affected. While the demand for ISUD treatment at specialized centers in Greece is well-documented, the role of private practice psychiatrists remains underexplored. The primary aim of this study was to investigate the extent to which private practice psychiatrists in Greece encounter and accept treatment requests primarily related to illicit substance use. The findings revealed that, among those who participated in the study, many private practice psychiatrists had encountered such treatment requests, with most reporting accepting them. However, given the exploratory nature of the study and the limited response rate, these findings should be interpreted with caution.

By shedding light on a critical component of the country's ISUD-related treatment landscape, this exploratory study suggests that a part of the treatment demand for ISUD in Greece is channeled towards private practice psychiatrists.

The demographic and geographical distribution of the study sample closely aligns with official national

data, supporting its representativeness. Specifically, 53% of participants were male and 47% female, which is comparable to the 2023 data from the Panhellenic Medical Association, indicating that, out of 1,730 specialized adult psychiatrists, 58.15% were male (n=1,006) and 41.85% female (n=724). Regarding geographic distribution, 59% of the participants in the

Table 4. Results of bivariate analyses examining the relationship between demographic and professional characteristics, as well as therapeutic practices, with (a) exposure to and (b) taking on treatment requests related to substance use among private practice psychiatrists.

Variables	Exposure to treatment requests (for the entire sample, n=100)		p-value	Taking on of treatment requests (among those who were exposed)*		p-value [†]
	Yes (84.0%, n=84)	No (16.0%, n=16)		Yes (69.0%, n=58)	No (31.0%, n=26)	
Gender						
Male	88.7	11.3	0.160	70.2	29.8	0.730
Female	78.3	21.7		66.7	33.3	
Age (years), M (SD)	49.9 (8.6)	47.8 (12.4)	0.407 [‡]	50.3 (8.7)	48.8 (8.4)	0.441 [‡]
Country of medical degree acquisition						
Greece	81.9	18.1	0.294	67.6	32.4	0.766
Outside Greece	94.1	5.9		75.0	25.0	
Educational level						
Bachelor's degree	81.5	18.5	0.306	61.4	38.6	0.110
Master's degree/Doctorate/Postdoctoral	88.9	11.1		77.5	22.5	
Country of medical specialty training						
Greece	85.6	14.4	0.535	70.1	29.9	0.671
Outside Greece	77.8	22.2		57.1	42.9	
	Exposure to treatment requests (for the entire sample, n=100)		p-value	Taking on of treatment requests (among those who were exposed)*		p-value [‡]
	Yes (84.0%, n=84)	No (16.0%, n=16)		Yes (69.0%, n=58)	No (31.0%, n=26)	
Training in a substance use treatment unit during specialty						
Yes	92.1	7.9	0.003	79.3	20.7	0.001
No	69.4	30.6		44.0	56.0	
Additional training in substance uses disorders beyond the specialty						
Yes	95.5	4.5	0.005	90.5	9.5	<0.001
No	74.5	25.5		46.3	53.7	
Practice setting						
Only private	85.2	14.8	0.726	65.2	34.8	0.403
Private and Public/NPO	82.6	17.4		73.7	26.3	
Current/Previous Employment in a substance use treatment facility						
Yes	97.4	2.6	0.004	86.5	13.5	0.002
No	75.8	24.2		55.3	44.7	
Years of practice as a private practice psychiatrist, M (SD)	13.8 (9.4)	13.0 (12.4)	0.763 [‡]	14.3 (9.4)	12.7 (9.5)	0.504 [‡]

Continues

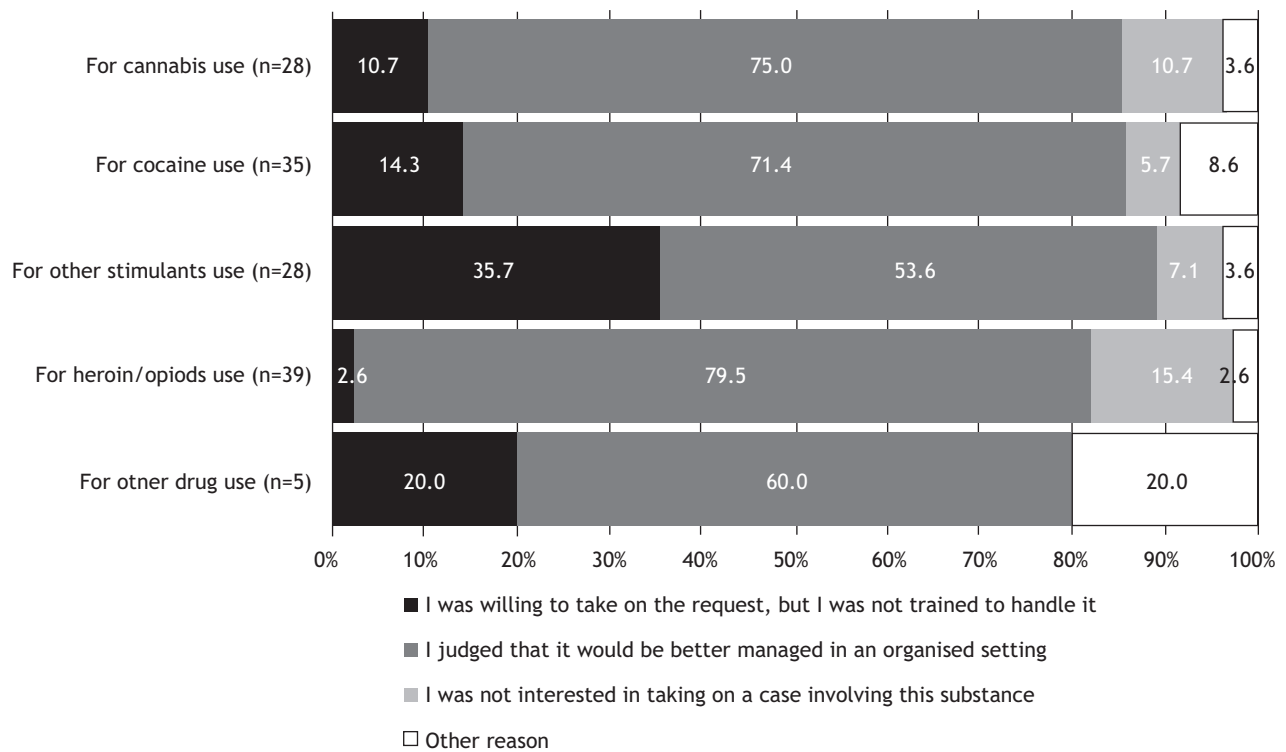


Figure 1. Reasons for declining treatment requests after exposure to them.

Table 5. Results of bivariate analyses examining the relationship between whether a private practice psychiatrist (a) has previously accepted a substance use treatment request and (b) is willing to accept the next similar request, by substance.

	Intention to accept future SUD treatment request	Intention to decline future SUD treatment request	p-value*
Regardless of the substance	(n=63)	(n=36)	
Has previously accepted a case	93.1	6.9	<0.001
Has never accepted a case	19.2	80.8	
Cannabis/ Cannabinoids	(n=61)	(n=38)	
Has previously accepted a case	94.2	5.8	<0.001
Has never accepted a case	25.0	75.0	
Cocaine/ Crack	(n=31)	(n=68)	
Has previously accepted a case	82.8	17.2	<0.001
Has never accepted a case	14.3	85.7	
Other stimulants	(n=16)	(n=83)	
Has previously accepted a case	50.0	50.0	0.005
Has never accepted a case	7.1	92.9	
Heroin/ other opioids	(n=13)	(n=84)	
Has previously accepted a case	90.0	10.0	0.017
Has never accepted a case	20.0	80.0	
Other substances	(n=24)	(n=75)	
Has previously accepted a case	63.6	36.4	<0.001
Has never accepted a case	94.2	5.8	

Note. *Fisher's exact test used unless otherwise specified

current study reported having a private practice in the region of Attica, 18% in Central Macedonia, and 23% in other regions of Greece. These figures are generally aligned with national statistics from 2023, which report that 49% of private practice psychiatrists were based in Athens (Attica), 17% in Central Macedonia, and approximately 33.87% in other regions. Findings showed that 84.0% of private practice psychiatrists who participated in the study encountered an ISUD treatment request in the past 12 months, with 58.0% accepting at least one. These results indicate that, apart from public addiction treatment centers, the affected individuals may seek and potentially receive treatment from private practice psychiatrists. This finding has important clinical implications, as it reveals that private psychiatric practices may serve as an alternative access point for ISUD treatment, particularly for individuals who may not meet admission criteria or prefer not to engage with structured public services. This underscores a need to strengthen addiction-related training for psychiatrists, both by enhancing the addiction curriculum during psychiatry specialty training and by offering targeted educational initiatives, including continuing professional development programs focused on the assessment and management of substance use. Such efforts could better equip office-based psychiatrists to respond appropriately to ISUD requests.

Ranked in order, psychiatrists received treatment requests for cannabis, cocaine, heroin/opioids, other stimulants, and other illicit substances. When comparing these findings with data from the 2022 Annual Drug Report, which estimated approximately 2,000 treatment requests for opioids, 1,000 for cannabis, and 500 for cocaine and stimulants, notable disparities emerge between treatment-seeking behaviors in private and public sectors.⁴ Specifically, opioid users may be more likely to seek treatment in public centers, while those using other substances may prefer private treatment. This likely reflects the lower socioeconomic status of opioid users, limiting access to private treatment, and their probable preference for substitution therapy, which is exclusively provided by public addiction services in Greece.^{3,17} This finding underscores the lack of structured pathways or guidance for ISUD care in private practice settings in Greece. This points to potential areas for policy development, such as the integration of addiction-focused resources or referral networks accessible to private practitioners. These additions would aim to strengthen the capacity of office-based psychiatrists to respond effectively and ethically to ISUD treatment demand.

An association was found between psychiatrists' exposure to treatment requests for illicit substance use

and their specialized training in addiction, experience working in specialized treatment facilities, and training in substance use departments during their specialty, while a trend toward a higher likelihood of encountering such treatment requests was observed among psychiatrists who self-reported specializing in addiction management. These findings align with prior studies that highlight the preference for psychiatrists with addiction expertise among individuals with SUDs.¹⁴

Additionally, an association was found between psychiatrists' acceptance of treatment requests and their specialized training in addiction, experience working in specialized addiction centers, self-reported specialization in addiction, and use of motivational interviewing. Psychiatrists most often accepted treatment requests for cannabis, "other substances" and cocaine use, followed by 'other stimulants', and least for heroin and opioids. This trend could reflect both clinical and contextual factors. For example, given the limited efficacy of pharmacotherapy for cannabis and cocaine use disorders,^{18,19} these cases may be viewed as more appropriate for outpatient, office-based psychosocial interventions, such as those offered in private psychiatric practices, and may motivate private practice psychiatrists to accept these requests.

The study also examined whether previous treatment-seeking behavior in specialized addiction treatment centers among patients who approached private practice psychiatrists was associated with the location of their practice, hypothesizing that psychiatrists outside urban centers would encounter more untreated patients due to accessibility issues.^{8,20,21} However, such an association was not supported, likely because both urban and rural areas in Greece have a sufficient number of public addiction treatment facilities, which may mitigate the impact of geographic location on treatment-seeking behavior.³

One-third of participants declined treatment requests, with most suggesting that these cases would be better managed in a structured setting. This finding is not consistent with previous research findings, which indicated a higher percentage of psychiatrists were not willing to accept such treatment requests.²² A further finding was that psychiatrists who had previously accepted ISUD cases were more likely to accept future cases, particularly those involving the use of cannabis and cocaine. Moreover, a positive association was found between prior acceptance of cases involving substance use by psychiatrists and their intention to accept similar subsequent cases, compared to their peers who had never accepted such cases before. This pattern likely reflects a familiarity or exposure effect, whereby repeated clinical

encounters with specific ISUD presentations enhance psychiatrists' confidence, perceived competence, and willingness to engage in treatment. Given that cannabis and cocaine were the most frequently encountered substances in this study, their higher acceptance rates may stem from increased clinical exposure, particularly in private practice settings where such cases are often managed through psychosocial interventions.

This study also examined the characteristics of accepted cases. Most psychiatrists reported that at least half of heroin/opioid users had previously sought treatment at public addiction centers, while the rate for other illicit substances was about one in ten. This finding reflects the barriers to accessing addiction services, as noted in previous studies.^{6,7,9,10,20,21} For cases involving cocaine and other stimulants, most psychiatrists reported that at least half the cases also abused alcohol. In contrast, for cases involving cannabis, heroin/opioids, about one-fifth of cases displayed alcohol abuse. These findings align with those of previous studies.^{23–27}

Additionally, most psychiatrists reported that around half of cannabis and 'other stimulants' users also abused other illicit substances. Regarding opioid and cocaine users, there was a near consensus among respondents that at least half cases were also abusing other illicit substances. These findings align with previous studies showcasing high levels of polysubstance use among substance users.^{28–34} The comorbidity rate of ISUDs with other mental health disorders was also investigated. Furthermore, most psychiatrists treating patients with cannabis, cocaine, or other stimulant use identified comorbidity, particularly with mood and personality disorders, in at least half of these cases. These findings align with previous research indicating increased treatment-seeking behavior in cases involving comorbidity.^{24,26,27,34–37}

The study also explored whether comorbidities and concurrent alcohol or polysubstance use influenced psychiatrists' willingness to accept similar future treatment requests. These correlations were not supported. However, psychiatrists with more experience treating opioid users with concurrent illicit substance use were more likely to accept future cases, possibly reflecting expertise in addiction management.

Regarding treatment approaches utilized, pharmacotherapy was used by most participants. This may reflect the high prevalence of comorbid mental disorders in those seeking treatment, as noted in prior studies.^{38–40} Among psychotherapeutic interventions, CBT and motivational interviewing were most utilized. The effectiveness of these interventions is supported by prior studies^{18,41–43} while a recent study suggests combining

pharmacotherapy with psychotherapy as the most effective.⁴⁴ This suggests that private practice psychiatrists who are equipped with diverse therapeutic tools may be better positioned to manage ISUDs in complex, comorbid presentations, which are frequently seen in private practice contexts.

Despite the study's low response rate, the findings offer valuable insights derived from psychiatrists with demonstrated interest or clinical exposure to ISUDs. Such participants probably represent the segment of private practice psychiatrists most likely to encounter and manage ISUD cases in real-world settings. Their responses thus provide expert-informed perspectives that enhance the study's relevance, particularly in the absence of prior national data on this topic. While the generalizability of findings is limited, their exploratory value remains substantial, offering initial insights into practice patterns, training needs, and system-level gaps. As such, the study provides foundational knowledge to inform future research, policy, and educational initiatives in office-based ISUD care.

While the study provides novel insights into an underexplored area, its findings should be considered considering several limitations. First, the relatively low response rate and sample size represent a significant limitation that may affect the generalizability of the findings. Such a low level of participation increases the risk that the sample is not representative of the broader population of private practice psychiatrists in Greece, and therefore, caution is warranted when attempting to extrapolate the findings, as estimates derived from this sample may not accurately reflect the attitudes or experiences of the general private psychiatric community. Although we aimed to assess a large sample of private practice psychiatrists and despite our efforts to increase participation, this low participation rate may be explained by specific factors related to the thematic focus of the study. Specifically, the field of addictions constitutes a specialized area within psychiatry, with a limited number of professionals having relevant experience and active involvement. Consequently, there might be a difference in characteristics between participating and non-participating psychiatrists, as those who were more experienced in treating ISUDs were probably more likely to respond. Moreover, the method of approaching participants via email assumes that the survey reaches only psychiatrists who regularly check their emails and are willing to participate, meaning that responses may not be random or fully representative of all psychiatrists in the country. This nonresponse bias could potentially exaggerate the prevalence of ISUD treatment demand in private psychiatric practice. Additionally, as HPA membership is voluntary, not all

private practice psychiatrists in Greece are registered with the association, further limiting the representativeness of the sample. Moreover, the study specifically focused on private practice psychiatrists and treatment requests addressed to them — a topic that may be perceived as private or sensitive — and this may have led some professionals to hesitate to take part due to the nature of their personal clinical practice. A second limitation lies in the inherent constraints of cross-sectional methodology, which allow for the identification of associations but preclude any inference of temporal sequence or causality between variables. Third, recall bias constitutes a notable limitation, as the study's data depended on participants' retrospective self-reporting of their experiences over the past 12 months. Such reliance on memory may have introduced inaccuracies or omissions, potentially affecting the validity and reliability of the reported exposure to and management of ISUD-related treatment requests.

Despite these limitations, the study's originality and the insights it provides help to balance these challenges. This is the first study in Greece to explore this topic,

shedding light on key information about the characteristics and services offered by private practice psychiatrists for ISUDs. For the first time, it was shown that illicit drug users in Greece seek treatment from both public addiction services and private practice psychiatrists. Psychiatrists were more frequently exposed to and accepted cases involving cannabis and cocaine use, while those who declined ISUD treatment requests most often reported that these cases would be better managed in a specialized setting. Future research should further explore the characteristics of patients treated for ISUDs in private settings, as well as the services provided to them, while policy and educational initiatives should be developed to support psychiatrists in private practice in managing such cases effectively.⁴⁵

Acknowledgments

The authors would like to acknowledge Konstantinos Kokkolis for his valuable comments on an early draft of the survey questionnaire. We also extend our gratitude to the Hellenic Psychiatric Association for disseminating the survey link to their members.

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Ερευνητική εργασία

Έκθεση και ανταπόκριση των ιδιωτών ψυχιάτρων στην Ελλάδα σε αιτήματα θεραπείας για τη χρήση παράνομων ουσιών: Έρευνα επισκόπησης συγχρονικού τύπου

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ΠΕΡΙΛΗΨΗ

Οι εξαρτήσεις σε παράνομες ουσίες αποτελούν μείζον πρόβλημα της δημόσιας υγείας. Τα άτομα με προβλήματα χρήσης ουσιών αναζητούν θεραπεία κυρίως σε εξειδικευμένες δομές απεξάρτησης, ωστόσο δεν είναι γνωστός ο ρόλος, η έκθεση και η ανταπόκριση των ιδιωτών ψυχιάτρων στην Ελλάδα σε πιθανά αιτήματα θεραπείας για τη χρήση ουσιών. Σκοπός της παρούσας εργασίας είναι η διερεύνηση της έκτασης της έκθεσης και του τρόπου ανταπόκρισης των ιδιωτών ψυχιάτρων σε αιτήματα θεραπείας για τη χρήση ουσιών, καθώς και η μελέτη των χαρακτηριστικών των ασθενών με σχετικά αιτήματα που απευθύνονται σε αυτούς. Πραγματοποιήθηκε συγχρονική μελέτη μέσω ανώνυμου ηλεκτρονικού ερωτηματολογίου, που απεστάλη στις ηλεκτρονικές διευθύνσεις ιδιωτών ψυχιάτρων την περίοδο Ιανουαρίου - Φεβρουαρίου 2024. Συνολικά ανταποκρίθηκαν 100 ιδιώτες ψυχίατροι, η πλειονότητα ήταν άνδρες (53%), με μέσο όρο ηλικίας τα 49,5 έτη (ΤΑ: 9,3) και 13,7 έτη επαγγελματικής εμπειρίας (ΤΑ: 9,9). Η πλειονότητα των συμμετεχόντων (84.0%) είχε εκτεθεί σε αίτημα θεραπείας για χρήση παράνομων ουσιών τους τελευταίους 12 μήνες, ενώ 69,0 % αυτών (58% του συνόλου) ανέλαβαν τέτοιο περιστατικό. Συχνότερα αναλήφθηκαν αιτήματα για κάνναβη και κοκαΐνη/κρακ. Επιπλέον, αναφέρθηκαν υψηλά ποσοστά συννοσηρότητας με άλλες ψυχικές διαταραχές, προβληματική χρήση αλκοόλ και πολλαπλή χρήση ουσιών στα αναληφθέντα περιστατικά. Συχνότερα προτιμήθηκαν η φαρμακοθεραπεία και η γνωσιακή συμπεριφορική θεραπεία ως θεραπευτικές επιλογές. Υψηλότερα ποσοστά ανάληψης είχαν οι ιδιώτες ψυχίατροι με ειδική κατάρτιση σε θέματα εξαρτήσεων ($p < 0,001$), με εμπειρία απασχόλησης σε δομή θεραπείας για χρήση ουσιών ($p = 0,002$), με αυτοαναφερόμενη εξειδίκευση στη διαχείριση περιστατικών χρήσης ουσιών ($p = 0,017$), με άσκηση στον χρόνο ειδικότητας σε τμήμα ουσιοεξαρτήσεων ($p = 0,001$) και όσοι εφάρμοζαν κινητοποιητική συνέντευξη ($p = 0,011$). Η πλειονότητα των συμμετεχόντων που δεν ανέλαβαν αιτήματα (~70%) έκριναν καταλληλότερη τη διαχείριση σε εξειδικευμένη υπηρεσία. Το 63.6% δήλωσαν ότι θα αναλάμβαναν μελλοντικό αίτημα -με σημαντικά υψηλότερο ποσοστό (93,1%) να αφορά όσους είχαν αναλάβει στο παρελθόν ανάλογο αίτημα, συγκριτικά με όσους δεν είχαν (19,2%, $p < 0,001$). Συμπερασματικά, φάνηκε ότι πέραν των εξειδικευμένων δομών, οι ιδιώτες ψυχίατροι στην Ελλάδα, επιπλέον, εκτίθεται και αναλαμβάνουν αιτήματα θεραπείας για τη χρήση ουσιών, με, συχνότερα να αφορούν σε χρήση κάνναβης και κοκαΐνης. Προτείνεται περαιτέρω μελέτη των χαρακτηριστικών των ασθενών με χρήση ουσιών που θεραπεύονται σε ιδιωτικά πλαίσια και των παρεχόμενων υπηρεσιών σε αυτούς.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Ιδιώτες ψυχίατροι, εξαρτήσεις, διαταραχές χρήσης ουσιών, αιτήματα θεραπείας, αντιλήψεις.

Research article

The evaluation of quality characteristics of the mental health services provided at the General Outpatient Psychiatry Clinic of the Eginition Hospital

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ARTICLE HISTORY: Received 15 January 2025/Revised 12 June 2025/Published Online 5 August 2025

ABSTRACT

This study aims to assess the quality characteristics of mental health services provided at the General Outpatient Psychiatry Clinic of the 1st Department of Psychiatry at Eginitio Hospital, with the objective of monitoring and improving care. It is a descriptive, cross-sectional study based on clinical records from 1,146 patients. From this total, a stratified random sample of 265 patients was selected and assessed using the Verona Service Satisfaction Scale (VSSS). Among the 1,146 patients, 52% were female. The most represented age group was 50–59 years. Additionally, 56% were unmarried, 47% were unemployed, and 42% lived with their parental family. Psychotic disorders were the most common diagnosis (38%). On average, patients attended three consultations annually, while 26% received more than four sessions per year. Increased visit frequency was significantly associated with both age ($p=0.001$) and psychiatric diagnosis ($p<0.001$). Regarding satisfaction, 84.2% of patients reported high satisfaction with services. Older age was positively associated with greater satisfaction levels ($p<0.001$). Concerning suggestions for service improvement, 28.7% of patients expressed a desire for access to psychotherapy, 25.3% requested more assistance in obtaining social benefits, and 20.8% supported the introduction of home treatment services. These findings align with previous studies in Greece, confirming slightly higher service use by women and a predominance of psychotic spectrum disorders. While the average follow-up interval was 120 days, medically necessary cases were monitored more frequently (30–90 days). Patient satisfaction was generally high, and older individuals tended to report greater contentment. Reported needs for service enhancement centered on increased access to psychotherapeutic and psychosocial interventions, along with the development of home-based care options.

KEYWORDS: Quality, mental health, patients' satisfaction, mental health services.

Introduction

Mental disorders require prolonged treatment and continuous follow-up, making the provision of high-quality mental health services essential. Effective care is a fundamental patient right, contributing both to improved clinical outcomes and the overall credibil-

ity of the healthcare system.^{1–3} Evaluation is intrinsically linked to quality and constitutes a prerequisite for improvement, as unmeasured aspects cannot be enhanced.⁴

International experience shows that evaluation criteria and indicators vary across countries due to

structural differences in mental health systems. The OECD has developed mental health quality indicators based on international data collection.⁵ In Greece, despite long-standing recognition of its necessity, systematic implementation of evaluation frameworks in mental health has been limited. Law 4715/2020 introduced key indicators such as safety, efficiency, responsiveness, accessibility, good governance, and resource management.⁶ In alignment with the European Parliament's Report (A9-0367/2023) and Resolution (2023/2074(INI)), current policy emphasizes the use of evidence-based tools and validated indicators for monitoring mental health data.⁷ The National Action Plan for Mental Health 2021–2030, particularly Axis 6, outlines strategic actions for developing protocols, guidelines, and indicators to assess the quality and safety of mental health services.⁸

The concept of healthcare quality has long been subject to diverse and occasionally conflicting interpretations. Nevertheless, at its core, it denotes the attainment of optimal outcomes through the delivery of health services that are effective, equitable, efficient, and patient-centered. Avedis Donabedian was instrumental in establishing the evaluation of healthcare quality as a distinct scientific discipline. He conceptualized care quality through three foundational dimensions: technical quality (the accuracy of medical procedures), interpersonal quality (the nature of the patient-provider relationship), and organizational/infrastructural quality (encompassing administrative and environmental conditions).⁹

Building on Donabedian's model, the World Health Organization (WHO) adopted the triptych framework of Structure, Process, and Outcome for evaluating health systems.¹⁰ Within this framework, Structure pertains to the settings, qualifications, and resources available, Process involves the actual delivery of care, and Outcome captures the effects of care on patients' health status. Each domain can be assessed through qualitative and quantitative indicators, facilitating systematic evaluation. Examples include average waiting times, appointment adherence rates, patient-reported satisfaction, and experiential feedback, all of which are integral to continuous quality improvement.

In this context, the present study focuses on the General Psychiatry Outpatient Clinic (GPOC) of Eginition Hospital, which is affiliated with the First Department of Psychiatry of the National and Kapodistrian University of Athens (NKUA). Eginition Hospital, where the First Department of Psychiatry is situated, is a tertiary mental health institution with many intervention and treatment management options for emergency cases, hos-

pitalization of patients with mental illness, as well as follow-up of ambulatory patients regularly. This study aims to systematically evaluate the quality of services provided at the GPOC, using well-established service evaluation indicators. It emphasizes both qualitative and quantitative metrics across the following key domains: Accessibility: e.g., waiting time for the initial appointment. Continuity of care: e.g., frequency of follow-up visits, percentage of patients attending consecutive appointments. Effectiveness: e.g., duration of sustained engagement in treatment, clinic utilization rates, patient satisfaction.

Data were collected through administrative records and standardized patient satisfaction tools. Indicators were selected based on relevance to international quality benchmarks and their applicability within the Greek healthcare context. The evaluation of these parameters is expected to yield critical insights into patterns of service utilization, patient adherence and retention, efficiency of the service, and perceived by patients quality of care. The ultimate goal is to provide services in accordance with the real needs and expectations of patients, which is a basic principle of modern healthcare systems. Although self-evident in theory, this aim is not uniformly implemented across health systems globally, particularly in countries with resource constraints or limited infrastructure for quality monitoring, such as Greece.

This research contributes to the international discourse on healthcare quality by presenting a data-driven evaluation from a Greek public mental health setting. Its findings are expected to highlight strengths and areas for improvement, provide a model for similar evaluations in other outpatient psychiatric services, and support evidence-informed policy decisions aimed at enhancing mental health care. Furthermore, the study underlines the ethical and institutional obligation of health services to implement quality assessment frameworks. Systematic evaluation based on transparent, evidence-based criteria not only enhances clinical outcomes but also fosters accountability, equity, and citizen trust in the health system. In conclusion, this research endeavors to demonstrate that: (1) Scientifically grounded quality assessment is feasible even in complex mental health settings. (2) Significant metrics can guide service development and resource allocation. (3) Greek mental health services have the willingness and capabilities to evaluate and improve the quality of their services. (4) National healthcare systems must institutionalize quality monitoring as a permanent function, and the state should evaluate them and pay them on the corresponding basis.

Materials and Method

Study design and procedures

The study type is descriptive, cross-sectional, and archival data-based. The population of reference consisted of patients registered and scheduled to visit the GPOC of the First Department of Psychiatry at Eginition Hospital between December 2022 and December 2023. All the above data were coded into an electronic file, along with data related to the frequency of sessions, attendance, and patients' absences over the last year. The study obtained permission from the hospital's Ethics Committee, permission to use the Greek-weighted questionnaire, and written informed consent was obtained from the respondent subjects for their participation in the study.

Research tools

Two tools were used for the research:

a. A structured data collection form was developed to record clinical, sociodemographic, and quality indicator variables, including gender, age, marital and employment status, diagnosis, treatment adherence, hospitalization history, and prescribed medication. An additional section captured accessibility and service responsiveness metrics (e.g., reason for attendance, number of visits, non-adherence).

b. The Greek-adapted version of the Verona Service Satisfaction Scale (VSSS-54),^{11,12} developed by the Medical School of the University of Ioannina,¹² was used. Fourteen items not applicable to GPOC services were excluded. The scale assesses seven dimensions: Overall Satisfaction (3 items), Professional Skills and Behavior (19), Information (3), Accessibility (1), Effectiveness (8), Types of Intervention (11), and Family Involvement (5).

Survey population and selection process

The reference population of the study consisted of patients considered as active in 2023 - registered and scheduled to visit the outpatient clinic that year (N: 2,019). From this population, the sample of the study was drawn as follows:

1. Clinical, sociodemographic data, and quality indicators were collected for 1,146 individual patients (58% of the active patients) who attended the GPOC during the study period. Data were obtained over consecutive two-month rotations in each outpatient office, through collaboration with the clinical team and review of medical records, reminder cards, and direct patient contact. Thus, the sample reflects all patients attending scheduled appointments within each two-month observation period.

2. From the initial pool of 1,146 patients, a subsample of 265 was selected using systematic stratified random sampling based on gender, representing 20% of daily appointments from each outpatient office. Patient appointments were recorded in an Excel file, including gender and registration number. The population was stratified by gender, and random numbers were generated to select 20% from each stratum. Selected patients were matched to registration numbers and recorded accordingly. In cases of non-attendance or refusal, the next eligible patient on the list was approached. The validated self-administered questionnaire "Verona Service Satisfaction Scale (VSSS-54)" was used to assess patient satisfaction.

Statistical analysis

For data analysis, the SPSS statistical application program version 26 was used. Normality testing was performed using the Kolmogorov-Smirnov method, skewness, and kurtosis testing. Where the data followed a normal distribution, parametric tests such as Student's t-test and analysis of variance (ANOVA) were used, while where the distribution was non-normal, the non-parametric Mann-Whitney U and Kruskal-Wallis H tests were used. A 5% statistical significance level ($p < 0,05$) was maintained for all analyses.

Results

According to our data files, 2,019 patients had requested reexamination scheduling at least once in 2023. From this inclusion population, 1,146 separate patients participated in the survey.

For the last years, strict adherence to the ministry's recommendations for sectorization has been followed. GPOC is designated to offer services at the 8th mental health sector with a reference population of 291,000 (adult population according to the 2011 ELSTAT census). According to the service's statistical data, the average waiting time for new patients' entry in 2023 was 21 days. The entry of new cases, according to a previous survey (2021) was at 25 days of waiting.¹³

Patients' clinical and sociodemographic characteristics are presented in table 1, and data on the frequency and characteristics of visits are presented in table 2.

The majority of patients belonged to the age group 50-59 years N: 297 (26%), N: 424 (37%) were from the 8th Sector of Mental Health (to which Eginition hospital belongs), N: 1,074 (94%) were receiving medication, and N: 717 (62.5%) of patients had previously had regular follow-up at another service. Of these, N: 399 (55.5%) were followed up privately. It was also found that more than half of the patients were single, N: 646 (56%), and

Table 1. Patients' clinical and sociodemographic characteristics.

		N	Percent %
Sex	Women	599	52%
Family status	Married	303	26%
	Unmarried	646	56%
	Divorced	145	13%
	Widowhood	52	5%
Working Status	Unemployed	542	47%
	Employed	226	20%
	Student - Undergrad	36	3%
	Pensioner	342	30%
Residence Status	Alone	278	24%
	Family	375	33%
	Paternal Family	483	42%
	In structure	10	1%
Diagnosis	Unemotional Psychosis	432	38%
	Affective Disorders	381	34%
	Anxiety Disorders	123	11%
	Other diagnoses	191	17%
Hospitalization in the Past	Yes	488	43%

Table 2. Data on the frequency and characteristics of visits.

Total Visits	1419
Average visits/day	18 reviews + 2 new patients
They did not attend the session	240 unique patients (21.5%) ¹
Patient sample	1146
New incidents	99 (30%) ²
Reference for hospitalization	3 patients relapsed (medication interruption)

1. In total 298 visits (21%)

2. Out of a total of 326 new patients in the year

Table 3. Data associated with the frequency of visits in 2023.

Frequency of attendance	Average	
	Median	Mode
Frequency of attendance: 4 or more /year (min 4-max 10)	338 (29.5%)	3 times/year
Patients who have never been absent during the year	669 (59.7%)	
Patients who have been absent 1 time during the year	335(29.9%)	
Patients who have been absent more than 2 times during the year	117 (10.2%)	
Patients who have attended only once during the year	223 (19.5%), 119 (53%), ¹ 103 (47%) ²	
Patients who have never come during the year	56 (4.9%)	

1. They only had 1 scheduled session

2. Had more than 1 scheduled session

lived either with their paternal family, N: 483 (42%), or alone, N: 278 (24%), and that a large percentage, N: 542 (47%), were unemployed. The medium frequency of follow-up in the GPOC was 3 times/year. Table 3 presents data on the frequency of visits in the particular year. The results indicated that the frequency of patient attendance was associated with age ($\chi^2=17.786$, $p=0.001$) and diagnosis ($\chi^2=56.588$, $p<0.001$), while the number of absences from regular follow-up was related to the work situation ($\chi^2=9.987$, $p=0.019$) (table 4).

A sample of 265 patients participated in the patient satisfaction survey of the services provided. The supplementary material file presents measures of centrality and dispersion of variables and the reliability index of the questionnaire. According to univariate analysis and exploration of differences between the questionnaire scales and the total questionnaire score concerning the clinical and sociodemographic characteristics of the sample, statistically significant differences were found in almost all scales. However, when linear regression was performed with the total questionnaire value as the dependent variable and all the patients' clinico-socio-demographic characteristics as the independent variable, it was found that the only statistically significant variable influencing the dependent variable at the level of statistical significance ($\beta=0.150$, $p=0.038$) was the age of the patients (table 5).

Discussion

The research findings highlighted useful conclusions that can be associated with the quality services provided by GPOC of the Psychiatric Clinic at Eginitieio Hospital, and can also be utilized for the implementation of specific interventions to improve quality at the service level.

The slightly higher attendance of women in mental health services, as observed in the present study, is consistent with previous findings from the same organization,¹³ where women submitted more requests for initial psychiatric evaluation. Similar trends have been reported in other Greek studies,¹⁴⁻¹⁹ supporting the notion that women are more affected by psychosocial stressors. Notably, a ten-year study by Pantelidou et al. demonstrated a statistically significant increase in men's service utilization following the economic crisis (from 38.5% during 2003-2009 to 43.9% during 2010-2015, $p<0.001$), potentially reflecting both the psychological impact of the crisis and a gradual shift in men's attitudes toward seeking mental health care.²⁰

The predominance of psychotic disorders in the current sample reflects the tertiary nature of the service, which primarily addresses severe and chronic psychiat-

Table 4. Investigation of the frequency of attendance and absences/year of the patients concerning their demographic characteristics

Frequency/year	1–3 Times % (N)	4–10 Times % (N)	0 Times % (N)	x ²	p
Age				17.786	0.001
<40	72.4% (160)	22.6% (50)	5.0% (11)		
40–59	60.0% (321)	35.5% (190)	4.5% (24)		
60+	69.3% (249)	25.3% (98)	5.4% (21)		
Diagnosis				56.588	<0.001
Psychotic Disorder	62.1% (266)	33.9% (145)	4.0% (17)		
Anxiety & Depressive Disorder	67.8% (251)	26.8% (99)	5.4% (20)		
Bipolar Disorder	48.6% (69)	47.9% (68)	3.5% (5)		
Other	80.4% (164)	12.7% (26)	6.9% (14)		
Absences/year	0 to 1 time	≥2 times		x ²	p
Working Status				9.987	0.019
Unemployed	87.8% (469)	12.2% (65)			
Employed	95.4% (207)	4.6% (10)			
Student – Undergrad	87.5% (28)	12.5% (4)			
Pensioner	88.8% (300)	11.2% (38)			

The values refer to absolute and relative frequencies (%), x² tests, and corresponding p-value. Bold typeface statistically significant differences are noted at the 5% significance level

Table 5. Linear regression of questionnaire VSSS total score and the patients' clinic–sociodemographic characteristics.

Variable	β	t	p	F	p	R ²
				3.932	0.002	0.087
(constant value)	4.255	18.236	<0.001			
Hospitalization	-0.125	-1.585	0.115			
Age	0.150	2.085	0.038			
Working Status	-0.001	-0.012	0.991			
Residence Status	-0.097	-1.900	0.059			
Years of cooperation	0.031	0.635	0.526			

Statistically significant differences at the 5% significance level are marked in bold

ric conditions. Similar patterns have been recorded in other tertiary psychiatric institutions in Greece¹⁸ and internationally, where schizophrenia is the most frequent diagnosis (40.6%), followed by bipolar disorder (21.2%) and depression (17.2%).²¹ In contrast, in primary mental health care settings such as the Vyrnas–Kaisariani Community Mental Health Center, anxiety and depressive disorders are more common,¹⁴ a pattern likely associated with the community-based approach and the typically milder symptomatology of patients. Likewise, in emergency departments, such as that of the General Hospital of Corfu, individuals who were suffering mood disorders accounted for 32%, compared to 23.1% for psychotic disorders.²² Finally, in the Mobile Mental Health Unit serving the remote Cycladic islands, the most frequent diagnoses were intellectual disability

(39.6%) and psychotic disorders (39.2%).¹⁵ This likely reflects limited access to specialized services and the accumulation of severe, untreated cases in geographically isolated areas with restricted mental health resources.

It was observed that a significant number of patients belonged to neighboring mental health sectors (32%), while 36% of the patients belonged to our mental health sector. In a previous survey,¹³ 3 years ago, requests from neighboring sectors for a first psychiatric assessment reached 39%, while from our Sector (the 8th sector) requests accounted for 18.6%. These results reflected the inadequacy of implementation strategies in the national sectorization plan. Following the above survey, our department implemented specific strategies to gradually streamline the patient inflow.

The average number of visits per day to the outpatient clinic's medical office was 18, with follow-up examinations and two new entry cases. According to psychiatric literature, a reasonable aim is to have approximately 10 patients treated and no more than 20.⁴ The average frequency of reassessments in our GPOC was found to be 3 times per year. Our results confirm data from other countries, as well as from Greece.^{18,23,24}

In our survey, 29.5% of patients attended 4–10 follow-up sessions annually, predominantly those with severe psychopathology. This suggests that when medically necessary, the service is capable of providing more frequent visits, as it was previously reported (range of 14–20% for such follow-up rates).²⁵ Investigating the frequency of follow-up examinations concerning age, our data revealed that patients aged 40–59 years needed more mid-year follow-up sessions than other age groups, consistent with some other surveys.^{19,26–28} However, not all international data confirm the same results.^{25,29} Follow-up frequency was also found to be diagnosis-dependent, with individuals diagnosed with bipolar disorder requiring more sessions annually (mean 4.8) compared to other groups. This suggests that patients' maintenance phase of bipolar disorder may necessitate more intensive monitoring, potentially due to the need for regular clinical and biological assessments targeting depressive and manic symptoms, sleep disturbances, suicide risk, comorbid substance use, medical conditions, and overall health concerns.^{30–32}

In the present study, 21.5% of patients failed to attend their scheduled psychiatric appointments, aligning with existing literature reporting non-attendance rates of approximately 20% in psychiatric settings—nearly twice that observed in other medical specialties.^{29,33–41} These rates vary widely depending on country, healthcare system, and service type, with some mental health services reporting non-attendance as high as 60%. Non-attendance is consistently identified as a clinical and systemic challenge, associated with increased hospitalizations and higher healthcare costs.^{39,41–44} A significant association was found between employment status and attendance: employed individuals had the lowest rates of missed appointments, while students had the highest. This may reflect either greater motivation for continuity of care among working individuals or unmet support needs. Targeted interventions, such as student-focused outpatient clinics with flexible scheduling and digital appointment reminders, may help address this issue.

Additionally, in 8.4% of cases, consultations occurred without access to the patient's medical file, highlighting administrative deficiencies in clinical documentation.

This compromises both care quality and clinician efficiency. The continued reliance on paper-based records is a key contributing factor, underscoring the urgent need for electronic health record implementation to support continuity of care and system efficiency.

In our survey, 227 patients (19.5% of the total) had only one examination, with 53% of them having just one scheduled session for the entire year. This result differs from the results of Petritzikis et al research in 2022,¹⁸ who reported that the percentage of patients who visited only once the GPOC at Alexandroupoli University Hospital in northeastern Greece was more than 50%. The author suggests that administrative factors, such as visits primarily for medical certificates, may explain this finding. In our survey, 10% of scheduled appointments were related to obtaining psychiatric certificates for administrative purposes. This difference may be attributed to the greater availability of psychiatric services in the large region of Attica compared to Northeastern Greece.

The evaluation of patient satisfaction with the services provided by the GPOC of the Psychiatric Department at Aiginiteio Hospital revealed a high overall level of satisfaction, in line with previous research in mental health settings.^{19,45,46} The highest scores were recorded in the 'Professional Skills and Behaviour' subscale, suggesting that the quality of the therapeutic relationship plays a key role in patient satisfaction. In contrast, the lowest scores were recorded in the "Types of Intervention" subscale, a result attributed to the methodological structure of the VSSS tool, which includes both services provided and not provided by the institution, potentially reflecting users' perceptions of unmet care.¹¹ Participants' responses highlighted specific unmet needs, most commonly: assistance in finding employment (20.4%), access to psychotherapy programs (28.7%), and support at home (20.8%). Additionally, some patients reported not receiving services that are theoretically available, such as support with social and vocational integration (14.7%) and guidance on accessing social benefits (25.3%). Similar findings were reported in the study by Mavroei et al, which also used the VSSS tool and identified unmet needs in individual (27%) and family sessions (33%), home assistance (17.3%), and welfare benefits (16.4%). These findings underscore the need to re-evaluate the scope of services provided and to strengthen interventions that respond directly to patients' expressed needs.

Univariate analysis indicated that age, marital status, employment, hospitalization history, and diagnosis were significantly associated with patient satisfaction, in line with previous findings.^{19,46–48} Gender, however,

showed no significant correlation, consistent with other studies.^{23,47–50} In multivariate analysis, age emerged as the sole statistically significant predictor of overall satisfaction. This positive association has also been confirmed by other researchers,^{45,47–53} suggesting that older patients tend to report higher satisfaction levels. This may reflect increased maturity, stabilized personal values, and greater familiarity with healthcare systems over time.⁵³

Conclusion

This study examined quality aspects of mental health services at the GPOC of the First Department of Psychiatry, NKUA. The average waiting time for a first visit was 21 days, with a mean attendance frequency of three times per year. More intensive follow-up (every 30–90 days) was offered to patients with complex clin-

ical needs. Consistent with prior Greek studies, women had slightly higher attendance rates, and most patients were diagnosed with psychotic spectrum disorders.

Overall, patient satisfaction was high, particularly in domains such as clinician competence, information, accessibility, and family involvement. Age significantly influenced satisfaction levels, in line with existing evidence. Patients expressed unmet needs in psychotherapy, psychosocial support, and home-based care, highlighting areas for potential service development. Despite high satisfaction, ongoing evaluation remains essential. Regular monitoring of quality indicators can inform targeted improvements. Evidence consistently links patient satisfaction with perceived service quality, emphasizing its role as a key performance metric. Future research should further explore outcomes related to effectiveness, responsiveness, and access.

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Ερευνητική εργασία

Διερεύνηση ποιοτικών χαρακτηριστικών των προσφερομένων υπηρεσιών στα Τακτικά Εξωτερικά Ιατρεία του Αιγινήτειου Νοσοκομείου

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ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 15 Ιανουαρίου 2025/Αναθεωρήθηκε 12 Ιουνίου 2025/Δημοσιεύθηκε Διαδικτυακά 5 Αυγούστου 2025

ΠΕΡΙΛΗΨΗ

Διερεύνηση ποιοτικών χαρακτηριστικών των υπηρεσιών ψυχικής υγείας που παρέχονται στα Τακτικά Εξωτερικά Ιατρεία της Α΄ Ψυχιατρικής Κλινικής του Αιγινήτειου Νοσοκομείου, με στόχο την παρακολούθηση και τη βελτίωσή τους. Πρόκειται για περιγραφική, συγχρονική μελέτη με στοιχεία αρχαιακής έρευνας καθώς αναλύθηκαν 1.146 ασθενείς. Από αυτό το δείγμα, επιλέχθηκαν 265 ασθενείς με στρωματοποιημένη τυχαία δειγματοληψία στους οποίους χορηγήθηκε η Ελληνική Έκδοση της κλίμακας Verona Service Satisfaction Scale (VSSS-54). Από το δείγμα 1.146 ασθενών, οι 599 (52%) ήταν γυναίκες, η κύρια ηλικιακή ομάδα ήταν μεταξύ 50-59 ετών, άγαμοι 646 (56%), άνεργοι 542 (47%), ζουν στην πατρική οικογένεια 483 (42%), με διάγνωση Ψυχωτική Διαταραχή 432 (38%). Η συχνότητα των επισκέψεων ήταν 3 φορές/έτος, ενώ το 26% των ασθενών είχαν περισσότερες από 4 συνεδρίες ετησίως. Η αυξημένη συχνότητα βρέθηκε να σχετίζεται με την ηλικία των ασθενών ($p=0,001$) και τη διάγνωση ($p<0,001$). Όσον αφορά στην εμπειρία ικανοποίησης από τις παρεχόμενες υπηρεσίες, 223 (84,2%) από τους ασθενείς ανέφεραν υψηλή ικανοποίηση. Όσο μεγαλύτερη είναι η ηλικία του ατόμου, τόσο υψηλότερο είναι το επίπεδο ικανοποίησης ($p<0,001$). Στα αιτήματα των ασθενών σχετικά με τη βελτίωση των υπηρεσιών, 76 (28,7%) επιθυμούσαν να κάνουν συνεδρίες ψυχοθεραπείας, 67 (25,3%) θα ήθελαν περισσότερη υποστήριξη για την απόκτηση κοινωνικών παροχών ενώ 55 (20,8%) εξέφρασαν την επιθυμία για υπηρεσίες κατ' οίκον θεραπείας. Τα ευρήματα της μελέτης σε σχέση με τα κλινικοδημογραφικά χαρακτηριστικά επιβεβαιώνουν τα ευρήματα άλλων μελετών όπου η συμμετοχή των γυναικών ήταν ελαφρώς υψηλότερη ενώ η πλειονότητα έπασχε από Διαταραχές Ψυχωτικού Φάσματος. Αν και η μέση συχνότητα προσέλευσης ήταν 120 ημέρες, όταν ιατρικά απαιτείτο, παρασχέθηκε πιο εντατική παρακολούθηση (30-90 ημερών). Σχετικά με την ικανοποίηση των ασθενών από τις παρεχόμενες υπηρεσίες, η πλειοψηφία ανέφερε υψηλή ικανοποίηση ενώ η ηλικία των ασθενών φάνηκε να επηρεάζει τον βαθμό ικανοποίησης. Σύμφωνα με τα αιτήματα των ασθενών περισσότερη ψυχοθεραπεία και ψυχοκοινωνική υποστήριξη καθώς και υπηρεσίες κατ' οίκον θεραπείας αναφέρθηκαν ως απαραίτητες.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Ποιότητα, ψυχική υγεία, Ικανοποίηση ασθενών, παρεχόμενες υπηρεσίες.

Research article

Compulsive buying-shopping symptoms in a Greek sample and their association with anxiety, stress, and depression: A cross-sectional online study

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ARTICLE HISTORY: Received 13 January 2025/Revised 3 June 2025/Published Online 20 December 2025

ABSTRACT

Symptoms of compulsive buying-shopping disorder (CBSD) are relatively common and have been associated with increased psychopathology, particularly mood and anxiety symptoms. However, relevant data are limited for the Greek population. We aimed to investigate the presence of CBSD symptoms in a Greek general population sample, and their potential association with anxiety, stress, depression, and demographic variables. A cross-sectional online study was carried out (October 2022 – November 2022) on 379 adults (females=254, 67%) from the general population from all over Greece. Participants were recruited using the snowball sampling method and completed a battery of questionnaires via Google Forms, including: (a) the “Compulsive Buying Scale” (CBS); (b) the 21-item “Depression Anxiety and Stress Scale” (DASS-21); and (c) the “Demographic Characteristics Questionnaire” – developed for the present research. Up to 19.5% of the sample’s subjects (N=74; females=60, 81.1%) demonstrated severe CBSD symptoms (CBS score>42.2) and were designated as belonging to the “high-CBSD-symptoms” group. The rest of the participants (N=305) demonstrated less severe CBSD manifestations (CBS score≤42.2) and were included in the “low-CBSD-symptoms” group. The mean age of subjects of the “high-CBSD-symptoms” group was 27 years (± 12.13 years). Significant positive correlations were found between CBS scores and all three DASS-21 subscales (stress, anxiety, depression). Particularly, subjects of the “high-CBSD-symptoms” group demonstrated significantly higher mean scores in all three DASS-21 subscales, compared to the “low-CBSD-symptoms” group. In regression analysis, higher stress levels, female gender, younger age, and residence in non-metropolitan areas significantly predicted more severe CBSD symptoms. The overrepresentation of women may limit generalizability. Furthermore, this study is cross-sectional, and therefore, it cannot assert that compulsive-buying symptomatology is a cause or consequence of anxiety, stress, or depressive symptoms. Finally, due to the nature of the study (online survey), no clinical data regarding psychiatric or medical history were collected. The present study suggests that severe CBSD symptoms may be prevalent in a significant proportion of the Greek population, especially in younger women, and are significantly associated with symptoms of anxiety, stress, and depression. Female gender, more intense stress, younger age, and living in non-metropolitan centers were predictors of more severe CBSD manifestations.

KEYWORDS: Anxiety, compulsive buying disorder, depression, stress, symptoms.

Introduction

Purchasing goods is an integral part of everyday life; however, in certain circumstances, purchasing behavior is associated with excessive distress and other psychopathological manifestations and may evolve into compulsive buying-shopping disorder (CBSD). Müller et al (2021) has demonstrated that psychopathological features of CBSD include time-consuming buying-shopping activities and consequent excessive spending, either online or in-person. The consumer items are essentially useless for the subject or are not utilized for the intended purposes. The subject has diminished control over these buying-shopping activities, which therefore persist despite the negative consequences; moreover, they interfere with other interests, leisure activities, and professional duties and cause significant distress and impairment in their personal, relational, professional, and other life domains, including the in-currence and escalation of financial debt.¹⁻⁶

According to Maraz et al (2016), the most recent meta-analysis estimated the prevalence rate of compulsive buying in general adult representative populations to be 4.9%.⁷ Female gender, younger age, and low-to-moderate income are factors associated with a higher prevalence of CBSD symptoms.⁸⁻¹¹ There are indications that CBSD symptoms are associated with other psychopathological manifestations, including stress, anxiety, and depression levels.¹² For example, the presence of a CBSD episode was associated with a greater number of stress-inducing daily events compared to other days¹³ and with a reduction, at least temporarily, of high levels of anxiety.¹⁴ Regarding etiology, symptoms of CBSD may share in common with other addictive disorders, the psychobiological mechanisms of reward.^{6,15}

Although international research has increasingly focused on the clinical and psychosocial correlates of Compulsive Buying–Shopping Disorder (CBSD), data from Southern European countries remain scarce, particularly from Greece. The current study aims to address this gap by providing preliminary epidemiological data on CBSD symptomatology in a Greek general population sample. While the mere absence of national data does not inherently justify a study, the value of culturally specific data lies in the known variability of compulsive buying behavior across countries due to sociocultural, economic, and psychological factors. Previous studies have demonstrated significant differences in the prevalence and expression of CBSD between countries with divergent economic trajectories, such as Greece and Turkey, and highlighted the role of national macroeconomic conditions in shaping

compulsive consumption patterns.^{16,17} Furthermore, a recent meta-analysis estimated the prevalence of CBSD at 4.9% in the general adult population, but acknowledged substantial heterogeneity across studies and regions. Given Greece's unique recent history of prolonged economic crisis and austerity, the psychological burden of financial stress, and shifting consumption norms, investigating CBSD in this cultural and socio-economic context is both timely and necessary. Our study, therefore, aims to contribute not only to national awareness and public health planning but also to the broader cross-cultural understanding of CBSD.⁸ Moreover, we investigated the potential associations of CBSD symptoms with demographic/socio-economic and clinical parameters – including manifestations of anxiety, stress, and depression. We hypothesized that there would be significant positive associations between CBSD symptoms and all three clinical dimensions.

Material and Method

Procedure

This was a cross-sectional online study from October 9 to October 31, 2022. The study's protocol was approved by the Ethics Committee of Eginition Hospital. All subjects provided informed consent. Sampling was based on convenience and the snowball method.¹⁸ Information sheets and questionnaires were created online using Google Forms and distributed through groups on the online platforms Facebook and Instagram. After reading the participation invitation and confirming their consent, individuals proceeded to complete the questionnaire. The study was anonymous, and participants disclosed only the personal information required by the study. All subjects were required to declare that they were 18 years of age or older. Inclusion criteria were: age ≥ 18 years old and voluntary agreement to participate in the research. Exclusion criteria were poor knowledge of the Greek language and not providing informed consent.

1. Demographic Characteristics Questionnaire (DCQ): This was created by the authors for this research; it concerns demographic/socio-economic parameters, including gender, age, place of residence, marital status, educational level, employment status, and monthly family income.
2. Depression Anxiety Stress Scale (DASS-21)¹⁹: The DASS-21 comprises three self-report scales – each comprising 7 items – designed to measure negative emotional states, including depression, anxiety, and stress, respectively. Each item is rated on a 4-point Likert scale (“0=not applicable to me at all” to “3=ap-

plicable to me very much or most of the time"). The total score is derived by doubling the scores of the subscales (total score range: 0-126). Higher scores indicate more intense symptomatology. The scale has been adapted to the Greek language by Lyrakos et al.²⁰ The internal consistency reliability for the entire scale is Cronbach's $\alpha=0.965$.

3. Compulsive Buying Scale (CBS)¹⁴: This is a 13-item self-report scale that measures thoughts, emotions, and behaviors related to compulsive buying. To our knowledge, no validated Greek version of the Compulsive Buying Scale (CBS) has been published to date. As the CBS is in the public domain and no formal permission is required for its translation or adaptation for research purposes, no additional authorization was necessary. The Greek version of the scale was administered to participants. The original English version of the questionnaire was translated into Greek by the first author. The translated version was then reviewed and revised by an expert in the field to ensure conceptual and linguistic accuracy. The scale has good reliability and validity. It utilizes a Likert-type scale (1= "Strongly disagree" to 5= "Strongly agree"). The total score ranges from 13-65. The CBS cut-off score commonly used in previous studies is 42.2; a score higher than 42.2 indicates that the person potentially suffers from CBS.

Statistical analysis

All statistical analyses were conducted using the statistical package SPSS v.28. Means and standard deviations (SD) were used to describe quantitative variables. Absolute (N) and relative (%) frequencies were used to describe qualitative variables. The Spearman's rank correlation coefficient (r) was used to assess the relationship between two quantitative variables.

To assess whether the quantitative variables followed a normal distribution, the Kolmogorov-Smirnov test was initially performed. In addition, the Shapiro-Wilk test was applied to Age, DASS-21 Stress, DASS-21 Anxiety, DASS-21 Depression, and CBS score. In all cases, the Shapiro-Wilk test yielded p-values <0.05 , indicating a violation of the normality assumption. Therefore, non-parametric tests (e.g., Mann-Whitney U) were applied for group comparisons.

Comparisons between groups for quantitative variables were performed using the Mann-Whitney U test, as the sample did not follow a normal distribution. Additionally, regression analysis was conducted to determine whether any of the variable(s) studied significantly predict the presence of CBSD symptoms. The level of statistical significance was set at $p\leq 0.05$.

In the present study, subjects with a CBS score >42.2 were included in the "high-CBSD-symptoms" group – i.e., a group with more severe CBSD symptoms, potentially meeting the criteria for a CBSD diagnosis –, while those with a CBS score ≤ 42.2 were designated as members of the "low-CBSD-symptoms" group.

Results

Demographic characteristics of the total sample

For research purposes, the participants' place of residence was recoded into two categories: metropolitan centers with a population exceeding 1 million inhabitants (including Athens and Thessaloniki, capital and co-capital of Greece, respectively) and non-metropolitan centers (including smaller urban and rural [towns, villages] centers).

A total of 379 participants from the general population of Greece took part in the study. Descriptive statistics for the total sample, as well as for the two subgroups based on compulsive buying symptoms (CBS score >42.2 vs. ≤ 42.2), are presented in table 1. Specifically, demographic characteristics (gender, age, place of residence, education, marital status, employment status, and monthly income) are reported for both the "high-CBSD-symptoms" and "low-CBSD-symptoms" groups. Between-group comparisons were conducted using Mann-Whitney U tests for continuous variables and chi-square tests for categorical variables.

Associations with depression, anxiety, and stress

The mean values and standard deviations of the CBS and the DASS-21 subscales "anxiety", "stress", and "depression" concerning all patients, and the "high-CBSD-symptoms" and "low-CBSD-symptoms" subgroups are presented in table 2.

Associations between CBSD symptoms and clinical and demographic parameters

A series of Spearman correlation analyses was conducted to examine the relationships between CBSD symptoms, as measured by the CBS score, and symptoms of depression, anxiety, and stress as measured by the respective subscales of the DASS-21. The results revealed statistically significant positive correlations across all dimensions. Specifically, CBSD symptoms were positively correlated with depressive symptoms ($\rho=0.248$, $p<.001$), anxiety symptoms ($\rho=0.297$, $p<.001$), and stress symptoms ($\rho=0.295$, $p<.001$). These findings suggest that higher levels of compulsive buying-shopping tendencies are associated with increased psychological distress across multiple domains (table 3).

Table 1. Comparison of Demographic and Clinical Characteristics between Participants with Low and High Compulsive Buying-Shopping Disorder (CBSD) Symptoms.

Characteristic	Low-CBSD Symptoms (N=305) N (%)	High-CBSD Symptoms (N=74) N (%)	Statistic χ^2 (DF)	p		
Gender						
Female	194 (63.6%)	60 (81.1%)	7.46 (1)	0.006		
Male	111 (36.4%)	14 (18.9%)				
Place of Residence						
Metropolitan Center	206 (67.5%)	45 (60.8%)	0.92 (1)	0.336		
Non-Metropolitan Center	99 (32.5%)	29 (39.2%)				
Education Level						
Postgraduate degree	60 (19.7%)	13 (17.6%)	1.80 (5)	0.875		
University degree	121 (39.7%)	29 (39.2%)				
Post-secondary education	29 (9.5%)	5 (6.8%)				
High school graduate	93 (30.5%)	27 (36.5%)				
Elementary school graduate	1 (0.3%)	0 (0.0%)				
PhD	1 (0.3%)	0 (0.0%)				
Marital Status						
Single	190 (62.3%)	42 (56.8%)	3.37 (4)	0.498		
Married	89 (29.2%)	21 (28.4%)				
Cohabiting	13 (4.3%)	6 (8.1%)				
Divorced	12 (3.9%)	5 (6.8%)				
Widowed	1 (0.3%)	0 (0.0%)				
Employment Status						
Unemployed	18 (5.9%)	7 (9.5%)	1.71 (6)	0.944		
Civil servant	66 (21.6%)	13 (17.6%)				
Private employee	104 (34.1%)	26 (35.1%)				
Self-employed	31 (10.2%)	8 (10.8%)				
Retired	4 (1.3%)	1 (1.4%)				
Homemaker	5 (1.6%)	1 (1.4%)				
Student	77 (25.2%)	18 (24.3%)				
Monthly Income						
No income	50 (16.4%)	10 (13.5%)			3.61 (4)	0.461
0-500 euros	91 (29.8%)	27 (36.5%)				
501-1000 euros	62 (20.3%)	19 (25.7%)				
1001-2000 euros	88 (28.9%)	15 (20.3%)				
>2000 euros	14 (4.6%)	3 (4.1%)				

Abbreviations: CBSD=compulsive buying-shopping disorder; DF=Degrees of Freedom

To investigate whether the mean scores of the DASS-21 subscales of stress, anxiety, and depression differ between the "high-CBSD-symptoms" group and the "low-CBSD-symptoms" group, the non-parametric Mann-Whitney U test was used, as the variables do not follow a normal distribution. The analysis revealed that subjects of the "high-CBSD-symptoms" group demonstrate significantly higher mean scores in all three examined DASS-21 subscales, compared to those of the "low-CBSD-symptoms" group (table 2).

Subsequently, a series of linear regression analyses were conducted to investigate potential predictors of

compulsive buying-shopping disorder (CBSD) symptoms, as measured by CBS scores. Three models were developed.

First, table 3 presents the results of a multivariate regression analysis in which the independent variables were the severity scores of the DASS-21 subscales for stress, anxiety, and depression. The model accounted for 10.1% of the variance in CBS scores ($R^2=0.101$). Among the predictors, only stress was a statistically significant contributor: for every additional unit increase in the "stress" subscale score, the CBS score increased by 0.217 units, holding all other factors constant. The

Table 2. Mean (\pm Standard Deviation) scores for CBS and DASS-21 subscales (Stress, Anxiety, Depression) for all participants, and for “Low-CBSD-symptoms” (CBS score ≤ 42.2) and ‘High-CBSD-symptoms’ (CBS score >42.2) groups. P-values from Mann-Whitney U tests compare DASS-21 subscale scores between the ‘Low-’ and ‘High-CBSD-symptoms’ groups.

Group	“Low-CBSD-symptoms” group (N=305)		“High-CBSD-symptoms” group (N=74)		Mann-Whitney results	
	Mean	SD	Mean	SD	U statistic	p
CBS	29.21	7.465	50.24	5.077	<0.001	<0.001
Stress (DASS-21)	14.22	9.771	19.08	10.332	8243.00	<0.001
Anxiety (DASS-21)	8.22	8.589	12.51	10.531	8538.50	0.001
Depression (DASS-SS-21)	10.98	10.329	14.54	10.800	8876.00	0.004

Abbreviations: CBS=compulsive buying scale; CBSD=compulsive buying-shopping disorder; DASS-21= Depression Anxiety Stress Scale-21

Table 3. Multivariate Regression Analysis of CBSD Symptom Severity. This table presents a multivariate regression model with CBSD symptom severity (CBS scores) as the dependent variable. Independent variables include the severity of stress, anxiety, and depression, as measured by their respective DASS-21 subscale scores. Spearman correlation coefficients (ρ) between CBS scores and DASS-21 subscale scores are also presented.

	Unstandardized Coefficients		Standardized Coefficients		95,0% Confidence Interval for B		Spearman correlation		
	B	Std. Error	Beta	t	p	Lower Bound	Upper Bound	Coefficients (ρ)	p (2-tailed)
Stress	0.217	0.092	0.199	2.367	0.018	0.037	0.397	0.295**	<0.001
Anxiety	0.177	0.093	0.148	1.897	0.059	-0.006	0.360	0.297**	<0.001
Depression	-0.011	0.082	-0.010	-0.131	0.895	-0.171	0.150	0.248**	<0.001

$R^2 = 0,101$

**Correlation is significant at the level 0.01 (2-tailed)

Abbreviations: CBS=compulsive buying scale; CBSD=compulsive buying-shopping disorder; DASS-21= Depression Anxiety Stress Scale-21

scores for the “anxiety” and “depression” subscales were not statistically significant in the multivariate model.

It is important to note that the predictor variables were moderately intercorrelated, and thus multicollinearity was present in the model. This is not unexpected, given that anxiety, depression, and stress are conceptually related psychological constructs, as reflected in their significant bivariate correlations. Therefore, the unique contribution of each variable in the regression model must be interpreted with caution, as multicollinearity may suppress or inflate individual effects.

Next, two hierarchical models were constructed to examine the predictive power of demographic variables. In table 4, all available demographic characteristics—gender, age, place of residence, education level, marital status, employment status, and monthly income—were entered simultaneously into a multiple linear regression model. This full model explained 6.5% of the variance in CBS scores ($R^2=0.065$). All predictors were retained in the model, regardless of their statistical significance in bivariate analyses, to assess the unique contribution of each factor while controlling for

the potential influence of the others. The methodology section and the caption of table 4 have been revised accordingly to reflect this analytical decision.

Additionally, bivariate associations between each demographic variable and CBS scores are also presented in table 4, using Spearman’s rank correlation for continuous variables (e.g., age). This dual presentation allows for a more comprehensive interpretation of the data by comparing unadjusted and adjusted relationships.

Discussion

The present study is the first, to the best of our knowledge, to investigate compulsive buying-shopping symptoms in a sample drawn from the general population of Greece, and to explore their potential association with psychopathological manifestations –including symptoms of stress, anxiety, and depression– and demographic parameters.

Almost 1 out of 5 (19.5%; N=74) participants of the study demonstrated significant CBSD symptoms and potentially suffered from CBSD (CBS score >42.2 ; “high-

Table 4. Multivariate regression analysis with dependent variable: CBSD symptoms (CBS scores) and independent variables: all demographic characteristics, and bivariate correlation between dependent and independent variables.

	Unstandardized Coefficients		Standardized Coefficients		95.0% Confidence Interval for B		Correlation*		
	B	Std. Error	Beta	T	p	Lower Bound	Upper Bound	Statistic	p (2-tailed)
Gender	-3.829	1.236	-0.165	-3.097	0.002	-6.260	-1.398	-0.161	0.002
Age	-0.140	0.060	-0.165	-2.326	0.021	-0.259	-0.022	-0.122	0.018
Place of Residence	-2.824	1.168	-0.122	-2.417	0.016	-5.120	-0.527	-0.127	0.013
Education Level	0.566	0.566	0.060	0.999	0.318	-0.547	1.679	-0.060	0.247
Marital status	0.673	0.817	0.050	0.824	0.411	-0.934	2.280	0.070	0.174
Employment status	-0.396	0.353	-0.073	-1.125	0.261	-1.090	0.297	0.033	0.527
Monthly income	-0.023	0.567	-0.002	-0.040	0.968	-1.137	1.091	-0.097	0.060

R²=0.065

Abbreviations: CBS=compulsive buying scale; CBSD=compulsive buying-shopping disorder

Demographic variable representation: Sex: 0: Female, 1: Male, Place of Residence: 0: Non Metropolitan Center, 1: Metropolitan Center, Education level: 0: Postgraduate degree, 1: University degree, 2: Post-secondary education, 3: High school graduate, 4: Elementary school graduate, 5: PhD, Marital status: 0: Single, 1: Married, 2: Cohabiting, 3: Divorced, 4: Widowed, Employment status: 0: Unemployed, 1: Public sector employee, 2: Private sector employee, 3: Self-employed, 4: Retiree, 5: Homemaker, 6: Student, Monthly income: 0: No income, 1: 0-500 euros, 2: 501-1000 euros, 3: 1001-2000 euros, 4: >2000 euros

*Spearman correlation used

CBSD-symptoms" group). Concerning all 379 patients of the sample, significant positive correlations emerged between the severity of CBSD symptoms (CBS score) on the one hand and the intensity of symptoms of stress, anxiety, and depression on the other (scores on the respective DASS-21 subscales). Particularly, subjects of the "high-CBSD-symptoms" group demonstrated more severe symptoms of stress, anxiety, and depression compared to those of the "low-CBSD-symptoms" group. Furthermore, higher stress levels (DASS-21) (but not those of anxiety or depression), female gender, younger age, and living in non-metropolitan centers predicted more severe CBSD symptoms.

The prevalence of CBSD reported in prior studies ranges between 1.8% and 8%, but may be as high as 16.2% in shopper-specific samples.^{1,11} The high percentage (19.5%) of subjects showing severe CBSD symptoms in our study may be because it corresponds to symptoms and not to the disorder per se. We do not know how many subjects of the "high-CBSD-symptoms" actually met the ICD-11 criteria for the diagnosis of CBSD.

Other reasons for the high percentage of subjects with severe CBSD symptoms in our study include the method of sampling, which was based on convenience and the snowball method, and the reduced representation of male subjects in the research (33% of the sample). Additionally, it is noteworthy that the sample mainly consisted of young individuals, who are more exposed to markets according to social norms.

In our study, the mean age of subjects of the "high-CBSD-symptoms" group is 27 years, in line with previous research, which indicates that the mean age of subjects demonstrating intense CBSD manifestations typically ranges between 18 and 30 years.²² Additionally, the high percentage of females included in our study's "high-CBSD-symptoms" group (81.1%) is also in line with percentages of females – up to 80–94% – previously found in samples of subjects with severe CBSD psychopathology.^{11,23} Moreover, according to our results, female gender is a predictive factor for the occurrence of more severe CBSD symptoms. This finding may be due to the fact that in females, buying and shopping behaviors are more linked to their recreational and social activities, compared to males, and thus they have a stronger symbolic and emotional role for the former compared to the latter.^{22,23}

Recent studies have also raised concerns about possible gender bias in the psychometric properties of compulsive buying-shopping scales. Found that certain items in the commonly used CBS scale may function differently across genders, potentially inflating female scores or underestimating male symptoms.

Although such analyses have not yet been conducted in Greece, similar item bias may exist in the Greek version of the CBS.^{24,25}

Regarding all patients of our sample, positive associations emerged between CBSD symptoms' severity and levels of anxiety, stress, and depression. This seems to be due to the significantly more severe symptoms of anxiety, stress, and depression of subjects of the "high-CBSD-symptoms" group compared to subjects of the "low-CBSD-symptoms" group.

Previous findings may help explain our study's results. Thus, a broad array of psychopathological manifestations, including symptoms of anxiety, depression, anger, loneliness, irritability, uncontrolled eating, and workaholism, has been associated and may potentially precipitate the emergence of compulsive buying.^{12,24–28} In these clinical contexts, compulsive buying may serve as a maladaptive means of relieving negative emotions in various situations.^{9,25,29} Indeed, a high percentage of compulsive buyers reported a positive change in their mood after making a purchase.³⁰ Thus, compulsive buying may serve as a strategy of mood regulation.²¹ On the other hand, it has been posited that most individuals with CBSD symptoms experience subjective distress in part because they feel unable to adequately control their behavior.¹¹ Notably, in a recent report, anxiety and emotion dysregulation consistently mediated the relationship between adverse childhood experiences and CBSD symptoms, while anxiety was a stronger predictor of CBSD symptoms compared to depression.³¹ From a biological perspective, pathological functioning of brain networks underlying reward processing, executive functioning, salience attribution, and habit formation, and of neurochemical systems including dopamine, serotonin, opioids, and other neurotransmitters, may contribute to the pathophysiology of CBSD symptoms.² Many of these neurobiological pathways may be common with those that underlie stress, anxiety, and mood manifestations.³²

Although all psychopathological dimensions (anxiety, stress, and depression) investigated in our study were positively associated with compulsive buying, only the stress levels in particular proved to predict the severity of CBSD symptoms. This is in line with the theoretical view that stress is closely related to addictive behavior, since it triggers "craving" reactions toward addiction-related stimuli; this "craving" contributes to the emergence of a habitual/compulsive behavior to rapidly provide relief, instead of a behavior under greater cognitive control.^{13,33,34} However, this relief is transitory and is replaced by an increase in anxiety or depression.^{35,36} Indeed, compulsive buying and shopping are

potentially a mediating factor for depression and other distress reactions.^{30,37} These ineffective mechanisms of coping contribute to the pathogenesis of compulsive buying as a behavioral addiction.²⁸ Despite these theoretical views, whether stress is an antecedent or a clinical correlate of CBSD is still not known.

The finding that stress –but not anxiety or depression– was the only significant predictor of CBSD symptom severity in our regression model warrants further discussion. A possible explanation may be found in the functional role of compulsive shopping as a coping strategy for immediate relief from distress. Individuals with compulsive buying tendencies often report that they engage in shopping to cope with negative emotions, avoid mistakes, and gain short-term emotional rewards. These motivations appear to align more closely with stress relief than with the broader emotional constructs of depression or anxiety. Conversely, it is also plausible that compulsive buying increases stress, due to financial strain, interpersonal conflict, or guilt, thus creating a reinforcing cycle. Longitudinal research is needed to clarify the temporal and potentially bidirectional relationships between stress and compulsive buying behavior.

Investigating the association between CBSD psychopathology and other clinical parameters is important, since anxiety, stress, and depression symptoms may all be targets for standard pharmacological and psychological interventions: their improvement may indirectly improve CBSD manifestations as well.

The limitations of the current study must be taken into consideration. The small number of male participants in the sample results in an overrepresentation of females, making it challenging to generalize the results. The underrepresentation of males may be attributed to the data collection process through Google Forms, where they might be less inclined to respond. However, we must stress that 80–94% of persons with CBSD manifestations in international research are female; more importantly, the results of a survey on the general adult population in the United Kingdom suggest that this gender difference is real and not an artifact of men being underrepresented in clinical samples as has been alleged.³⁸ Furthermore, this study is cross-sectional, and therefore, it cannot assert that compulsive buying is a cause or consequence of anxiety, stress, or depression. Finally, due to the nature of the study (online survey), no data were obtained regarding clinical and treatment parameters, including history of mental disorders, non-psychiatric medical conditions, alcohol/substance use disorders, and current/past (psycho)pharmacological/psychological treatments. Moreover,

the sample was collected using snowball sampling, which can introduce bias and limit the generalizability of the findings. Future studies should address these limitations and further illuminate the complex association of compulsive buying-shopping psychopathology with symptoms of stress, anxiety, and depression.

Conclusion

The present study suggests that severe CBSD symptoms may be prevalent in a significant portion of the Greek population and are associated with symptoms of anxiety, stress, and depression. Higher stress levels,

female gender, younger age, and living in non-metropolitan centers predicted more severe CBSD symptoms. Female gender, younger age, and residence in non-metropolitan areas were significant predictors of more severe symptoms. These findings align with international literature but also highlight the importance of considering cultural and socioeconomic factors, such as Greece's recent economic context. Our results provide preliminary evidence to inform public health strategies and contribute to the broader cross-cultural understanding of CBSD, while future research is needed to confirm and extend these observations.

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Ερευνητική εργασία

Συμπτώματα διαταραχής καταναγκαστικών αγορών σε δείγμα ελληνικού πληθυσμού και η συσχέτισή τους με εκδηλώσεις άγχους, στρες και κατάθλιψης: Συγχρονική διαδικτυακή μελέτη

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ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 13 Ιανουαρίου 2025/Αναθεωρήθηκε 3 Ιουνίου 2025/Δημοσιεύθηκε Διαδικτυακά 20 Δεκεμβρίου 2025

ΠΕΡΙΛΗΨΗ

Τα συμπτώματα της διαταραχής καταναγκαστικών αγορών (ΔΚΑ) (compulsive buying-shopping disorder) είναι αρκετά συχνά στον γενικό πληθυσμό και μπορεί να συνδέονται με αύξηση ψυχοπαθολογικών εκδηλώσεων, και ειδικότερα των συμπτωμάτων κατάθλιψης και άγχους. Ωστόσο, δεν υπάρχουν επαρκή δεδομένα για τον ελληνικό πληθυσμό. Σκοπός της μελέτης ήταν η διερεύνηση της παρουσίας συμπτωμάτων της ΔΚΑ σε δείγμα του γενικού πληθυσμού της Ελλάδας και η ενδεχόμενη συσχέτιση τους με συμπτώματα άγχους, στρες και κατάθλιψης και δημογραφικές παραμέτρους. Διεξήχθη συγχρονική μελέτη (Οκτώβριος-Νοέμβριος 2022) και το δείγμα απαρτιζόταν από 379 ενήλικα άτομα (γυναίκες=254, 67%) από τον γενικό πληθυσμό όλης της Ελλάδας. Η δειγματοληψία πραγματοποιήθηκε μέσω της μεθόδου της χιονοστιβάδας και οι συμμετέχοντες συμπλήρωναν μέσω Google forms τις εξής κλινικές-ψυχομετρικές δοκιμασίες: (α) "Compulsive Buying Scale" (CBS), (β) "Depression Anxiety and Stress Scale" – 21 λήμματα (DASS-21) και (γ) "Demographic Characteristics Questionnaire" – το οποίο δημιουργήθηκε για τους σκοπούς της παρούσας μελέτης. Ποσοστό 19,5% των συμμετεχόντων (N=74, γυναίκες=60, 81,1%) παρουσίαζαν σοβαρά συμπτώματα ΔΚΑ (CBS σκορ >42,2) και συμπεριελήφθησαν στην ομάδα «ΔΚΑ-ΝΑΙ». Οι υπόλοιποι συμμετέχοντες (N=305) παρουσίαζαν μικρότερης σοβαρότητας συμπτώματα ΔΚΑ (CBS σκορ ≤42,2) και συμπεριελήφθησαν στην ομάδα «ΔΚΑ-ΟΧΙ». Η μέση ηλικία των ατόμων της «ΔΚΑ-ΝΑΙ» ομάδας ήταν 27 έτη (±12,13 έτη). Παρατηρήθηκαν στατιστικά σημαντικές συσχετίσεις μεταξύ του σκορ στην κλίμακα CBS με τα σκορ και των τριών υποκλιμάκων της DASS-21. Ειδικότερα, άτομα της «ΔΚΑ-ΝΑΙ» ομάδας παρουσίασαν σημαντικά υψηλότερα σκορ και στις τρεις υποκλίμακες της DASS-21 συγκριτικά με άτομα της «ΔΚΑ-ΟΧΙ» ομάδας. Τα υψηλότερα επίπεδα στρες, το γυναικείο φύλο, η μικρότερη ηλικία και η διαμονή σε «μη μητροπολιτικές» περιοχές αποτελούσαν σημαντικούς προγνωστικούς δείκτες παρουσίας σοβαρότερων συμπτωμάτων ΔΚΑ. Περιορισμό αποτελεί η υπεραντιπροσώπηση γυναικών και η συγχρονική φύση της μελέτης, καθώς δεν τεκμηριώνει αιτιακή σχέση των συμπτωμάτων ΔΚΑ και των συμπτωμάτων άγχους, στρες και κατάθλιψης. Επίσης, επειδή η μελέτη διεξήχθη διαδικτυακά, δεν κατέστη δυνατή η συλλογή άλλων κλινικών παραμέτρων. Τα αποτελέσματα της παρούσας μελέτης υποδηλώνουν ότι τα συμπτώματα ΔΚΑ μπορεί να είναι συχνά στον γενικό πληθυσμό και συσχετίζονται σε σημαντικό βαθμό με την παρουσία συμπτωμάτων άγχους, στρες και κατάθλιψης. Τα υψηλότερα επίπεδα στρες, το γυναικείο φύλο, η μικρότερη ηλικία και η διαμονή σε μη μητροπολιτικές περιοχές αποτελούσαν παράγοντες πρόβλεψης σοβαρότερων εκδηλώσεων συμπτωμάτων ΔΚΑ.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Άγχος, διαταραχή καταναγκαστικών αγορών, κατάθλιψη, στρες, συμπτώματα.

Review

A systematic review of the efficacy of CBT on pain and sexual function of vulvodynia

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ARTICLE HISTORY: Received 20 February 2025/Revised 9 June 2025/Published Online 5 August 2025

ABSTRACT

Vulvodynia is an underdiagnosed pain syndrome with persistent duration, usually without an identifiable organic cause. It negatively affects the quality of life, mental health, and romantic relationships and sexual function of women. This review aimed to systematically appraise the available data on the effectiveness of Cognitive Behavioral Therapy on perceived pain and sexual functioning of women with vulvodynia from randomized clinical trials irrespective of their time of publication. The review was performed following the PRISMA guidelines. The literature search was conducted based on specific eligibility criteria in the PubMed, PsycInfo, and Scopus databases using appropriate keywords. The methodological quality of the included studies was assessed with the Jadad Scale. The search resulted in 10 randomized clinical trials that compared the effectiveness of Cognitive Behavioral Therapy compared to other psychotherapeutic approaches and clinical, pharmaceutical, and surgical interventions on 835 women with vulvodynia. The results, which were synthesized narratively based on intervention type and outcomes assessed, revealed the superiority of Cognitive Behavioral Therapy compared to topical treatments with significant improvements in sexual function and pain management, particularly evident at follow-up assessments. Comparisons with other psychotherapeutic approaches (mindfulness-based cognitive therapy, supportive psychotherapy) resulted in similar results. Compared to physiotherapeutic and surgical protocols, Cognitive Behavioral Therapy resulted in more favorable findings, although the improvement regarding sexual function was significant mostly at the 6-month follow-up measurements. Cognitive Behavioral Therapy appeared to help by restructuring dysfunctional beliefs, reducing pain catastrophizing, and developing alternative pain coping strategies. Despite the encouraging evidence, variations with respect to the cognitive-behavioral interventions, comparison groups, and assessment tools used to assess the variables under investigation, direct comparison of the findings was challenging. The results highlighted Cognitive Behavioral Therapy as a promising, non-pharmacological approach to the management of vulvodynia. Education of psychotherapists and clinicians, particularly gynecologists, would contribute to early diagnosis and effective treatment of vulvodynia.

KEYWORDS: Vulvodynia, cognitive behavioral therapy, vulvar pain, female sexual function, randomized control trial, systematic review.

Introduction

Vulvodynia refers to vulvar pain with a duration of at least three months and without a specifically identified cause.¹ It can be either localized to one area, generalized to multiple areas, or mixed. It can be provoked (e.g., vaginal penetration), spontaneous, or mixed. The onset of vulvodynia could be classified as either primary (e.g., during the first intercourse) or secondary (occurring later in life). Regarding the pain pattern, this can be either continuous or constant, rhythmic or intermittent, and transient or brief.² Its prevalence has been estimated at 8%,^{3–5} while its incidence is over 4 cases per 100 person-years, with younger women appearing as more vulnerable (7.6 cases per 100 person-years at 20 years of age, compared with 3.3 cases per 100 person-years at 60 years of age).⁶

Vulvodynia affects women's health-related quality of life,⁷ their psychological well-being and romantic relationships,⁸ while the pain's chronicity may cause physical disability.⁹ One of the main domains affected is sexual health; it increases sexual distress and reduces sexual satisfaction and function.¹⁰ One of the main reasons for its impact is the lack of proper and timely treatment. In the US, 40% of women with relevant symptomatology choose not to seek treatment, while 60% of those who do seek help visit at least three clinicians before receiving the correct diagnosis.³ Regarding Europe, only 10–25% receive the correct diagnosis as 40–65% of gynecologists have no relevant diagnostic knowledge, and 20% of them support that their specialty is not the one to initiate treatment.¹¹

The heterogeneity of vulvodynia patients creates a significant challenge in the identification of a "gold standard" treatment approach. To date, the treatment of choice largely depends on expert opinion. Its treatment includes pharmacological and/or non-pharmacological interventions, while for some cases, surgical procedures are performed. Regarding the pharmacological regimens, these include topical (e.g., lidocaine, gabapentin, or amitriptyline cream, botulinum toxin injections), vaginal (e.g., diazepam suppositories), and oral (e.g., oral amitriptyline or gabapentin, antifungals) medication. However, even under medication, women self-report a 6.7/10 pain intensity in relevant instruments, 60% of them consume alcohol, and 43% combine alcohol and analgesics (including opioids) to reduce pain.¹² Concerning surgical procedures, vulvar vestibulectomy is recommended when typical, non-invasive procedures are ineffective.^{13,14} However, when comparing conservative and surgical interventions, pain and sexual function outcomes are similar,¹⁴ implying that the non-invasive treatment is preferable.

Among the non-pharmacological treatments, pelvic floor physical therapy,¹⁵ acupuncture,¹⁶ hypnotherapy,¹⁷ and fractional CO₂ laser therapy¹⁸ consists of alternative approaches. Yet, the efficacy of the first three approaches still requires further investigation with RCTs, while the FDA warns against the use of energy devices for vulvodynia due to possible adverse effects.¹⁹

Given the low efficacy and side-effect profile of medications for vulvodynia, attention has shifted towards psychological interventions, mostly over the past decade. Cognitive behavioral therapy (CBT) aims to challenge maladaptive thoughts regarding pain, disrupt avoidant behaviors, manage catastrophizing, and enhance coping mechanisms.²⁰ The present study aimed to systematically appraise randomized clinical trials regarding the efficacy of CBT on vulvodynia in terms of pain and sexual function.

Material and Method

The study was designed according to the PRISMA statement guidelines.²¹ This systematic review was not registered in any prospective review registry. Stages of research incorporated problem formulation, thorough search of the existing research, data extraction and quality evaluation, and, lastly, data analysis and presentation. Studies included in this review followed specific inclusion/exclusion criteria as indicated below.

Eligibility criteria

The studies had to investigate the efficacy of CBT on vulvodynia in adult women irrespective of its type. For this review, interventions were considered as CBT if they incorporated core cognitive-behavioral principles, including psychoeducation, cognitive restructuring, behavioral strategies for pain management, and skills training. Diagnosis of vulvodynia had to be established by a gynecological examination and not self-reports. The primary outcome of interest had to be perceived pain and sexual function. The comparison interventions and the CBT protocol did not constitute reasons for exclusion, while the studies had to report the protocol's details (duration, number of sessions, etc.). The studies had to be published in the English language by peer-reviewed journals. Research protocols without providing sufficient data were not included. The time of publication did not constitute a criterion of exclusion.

Search strategy

Pubmed, Scopus, and PsycInfo databases were thoroughly searched for relevant studies from the 1st until the 28th of November 2024. Research was conducted

by two reviewing investigators, using the following terms: “vulvodynia” OR “vulvar pain” AND “CBT” OR “cognitive behavior therapy” OR “cognitive behavior treatment” OR “cognitive behavior intervention” AND “efficacy” OR “outcomes”, and were adopted accordingly when necessary. Titles, keywords, and abstracts of each study were screened for eligibility. All eligible studies were managed and documented using the Zotero reference management software. A backward search (hand search of reference lists) of included papers was conducted to identify additional studies relevant to the topic. All studies were assessed according to the eligibility criteria.

Data extraction

Summary tables were developed to display key features of the included studies, such as study design, population characteristics, comparator type, CBT format, and reported outcomes related to pain and sexual function. These tables facilitated subgroup comparisons and enhanced the transparency of the synthesis process. In addition, a PRISMA 2020 flow diagram was used to visually represent the study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final synthesis. For each outcome of interest (pain and sexual function), effect measures as reported in the original trials were extracted. These typically included mean differences, standard deviations, and p-values for between-group and within-group comparisons. No data transformation or statistical imputation was required for the synthesis. All included studies reported complete outcome data, and no conversions or estimations of missing summary statistics were necessary. Included studies were grouped for narrative synthesis based on the type of comparator intervention (e.g., pharmaceutical, surgical, psychotherapeutic, or physical therapy) and the format of CBT delivery (individual, group, or couple-based).

Quality evaluation

Methodological quality assessment was performed independently by two researchers with the modified version of the Jadad scale,²² as described in previous research.²³ The scale evaluates 8 domains regarding the methodological soundness of each study: randomization, blinding, withdrawals, dropouts, inclusion/exclusion criteria, description of possible adverse effects of the implemented interventions, and statistical analyses. The total score is computed by summing the score of each item, with the total score ranging between 0 to 8. A study receiving a total score between 0 to 3 is con-

sidered of low quality, whereas total scores between 4 and 8 indicate a methodological approach of high quality.

Results

Study selection process

The initial search yielded 87 potentially eligible studies. After removing duplicates and screening 56 titles and abstracts based on the eligibility criteria, 32 articles were fully assessed. The final step of research resulted in 10 RCTs. The detailed screening procedure is illustrated in figure 1.

Basic characteristics of the included studies

The studies were RCTs, conducted primarily in Canada, with two of them coming from the United States and Sweden, and held between 2001 and 2021. All the included studies evaluated the effectiveness of CBT for adult women with vulvodynia. In total, 835 women with the diagnosis were included. All studies used the diagnostic criterion of a gynecological examination with a cotton swab test. The mean age ranged from 26.4 to 43.0 years. Among the included studies, six implemented group CBT sessions,^{24–29} two of them provided individualized sessions,^{30,31} while in two couples CBT treatment was implemented.^{31,32} In the majority of the studies, CBT involved focusing on psychoeducation, cognitive restructuring techniques, communication techniques, and pain management. Intervention protocols lasted between eight and 13 weeks, and each session had a duration of 60 to 150 minutes. When implemented in group settings, interventions were held in groups of 5–10 people. Concerning the comparison groups, four of them included topical treatments (lidocaine, corticosteroids),^{24,29,31,32} one of them applied a physical therapy intervention,³⁰ three of them implemented mindfulness-based cognitive therapy,^{26–28} one of them vestibulectomy and biofeedback,²⁵ and one supportive psychotherapy session.³⁰ All of the included studies assessed pain intensity and female sexual functioning and related psychological characteristics, such as pain anxiety,²⁷ catastrophizing pain,^{24,26–30,32} and pain coping strategies.³⁰ Secondary psychological characteristics, such as pain tolerance,³⁰ self-efficacy,²⁹ and personality characteristics²⁸ were also assessed in a portion of the studies. One of the studies performed measurements that referred to the partner’s perception of pain,³¹ while one study evaluated both partners’ sexual function.³² Measurements were performed with the use of self-report instruments, while one study used a vulvalgesiometer for pain assessment.²⁷ The synthesis relied on the statistical information provided

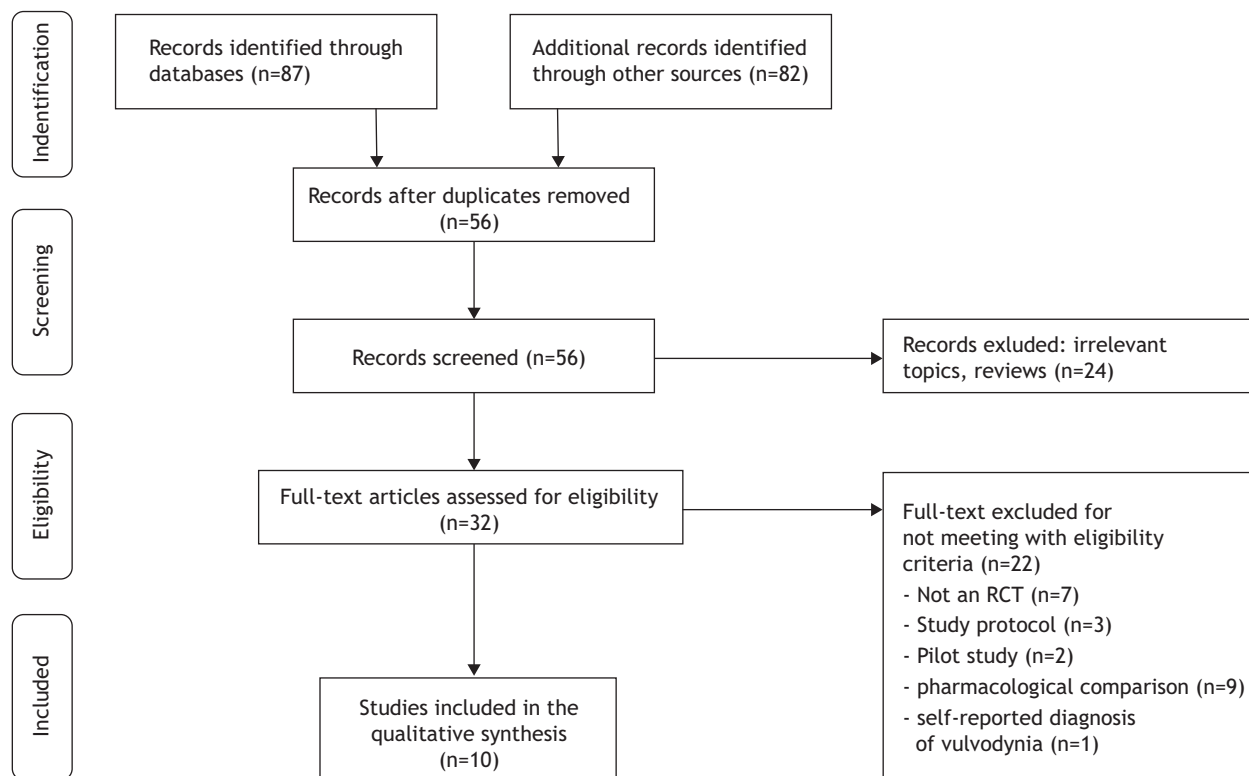


Figure 1. Flow diagram of the study selection process.

in each study. Summary statistics (e.g., *p*-values) were extracted where available. However, standardized effect estimates (e.g., Cohen's *d*, confidence intervals) were not consistently reported across studies and were therefore not recalculated. The basic characteristics of the included studies are presented in table 1.

Main results based on research questions

Three of the included studies examined the comparative effectiveness of CBT and mindfulness-based CBT (MBCBT) psychotherapy. Two of these studies reported significant post-treatment improvements in sexual function for both intervention groups ($p < 0.001$).^{26,28} However, these effects remained statistically significant at the six-month follow-up in only one study.²⁶ Furthermore, the same study found comparable improvements between the groups across all other measured outcomes, including psychological functioning and perceived change. Notably, self-reported pain reduction was greater in the mindfulness-based cognitive psychotherapy group.²⁶ The third RCT comparing CBT and MBCBT found that those with higher baseline pain reported the greater reductions regardless of treatment. However, women with longer relationships, as well as women with primary vulvodynia in the CBT arm, reported greater reduction. It was also reported

that the relationship length moderated sexual function ($p < 0.01$).²⁷ Women in shorter relationships improved more with MBCBT, whereas women in longer relationships improved more on sexual function with CBT. Masheb and colleagues compared CBT and supportive psychotherapy. With respect to pain severity during physical examination, this was significantly reduced to a greater degree for the CBT arm ($p = .014$).³³ In addition, results reported a significantly greater improvement in sexual function ($p = .034$) pre- to post-treatment.³³

Regarding the four studies that compared CBT with topical treatments, results were contradictory, with a tendency in favor of CBT. Three of them reported better sexual function for the CBT group. This improvement was noted only for the CBT group at the post-treatment measurement by one study ($p = 0.000$),³¹ and this was greater for women whose partner demonstrated higher levels of anxiety ($p < 0.01$) and for women with lower sexual goals ($p = 0.001$).³¹ The second study resulted in a significant difference in sexual function in favor of the CBT groups, but only 6 months post-treatment.²⁴ The third RCT yielded significantly more improvements for the CBT arm in pain unpleasantness ($p < .001$) at 6-month follow-up, pain anxiety ($p < .001$) and pain catastrophizing at post-treatment and 6-month follow-up, and sexual distress at post-treatment ($p < .001$).³² The

Table 1. Basic characteristics of the included studies (N=10).

Study characteristics	Sample's characteristics [total N, mean age, (SD)]	Intervention (N)	Comparison (N)	Measurements	Main results
Bergeron et al 2016, Canada ²⁵	N=69, 26.9 (6.09)	N=39, 10 2-hrs group CBT sessions for 13 weeks (7-8 women/group). Psychoeducation, Kegel exercises, communication skills, cognitive restructuring	N=30, twice daily application of 1% hydrocortisone cream for 13 weeks, educational material on vulvodynia	MPQ, FSFI, PCS, PISES	Both groups reported significant improvements post-treatment. The CBT group reported significantly reduced pain (p=0.03) and better sexual function (p = 0.01) at the 6-month follow-up compared to the topical treatment group.
Bergeron et al 2001, Canada ²⁴	N=78, 26.8 (5.4)	N=24, 8.2 hrs group CBT sessions for 12 weeks. Psychoeducation, Kegel exercises, communication skills, and cognitive restructuring	N=22, vestibulectomy (30' surgical procedure under general anesthesia-excision of the ves-tibular area to a 2 mm depth & 1 cm width); N=25, sEMG bio-feedback (contractions & rest periods)- training in the use of a portable sEMG home trainer for daily practice sessions.	MPQ, Global Sexual Functioning score (Sexual History Form), FSFI, BSI-GSI	At posttreatment, vestibulectomy participants had significantly lower pain levels than both group CBT, (p<0.01), and biofeedback participants (p<0.01). The significance was maintained at the 6-month follow-up (p<0.01). Participants from all three treatments improved significantly from pre-treatment to 6-month follow-up (p<0.01).
Bergeron et al 2021, Canada ²²	N=108 (& partners) (27.0) (6.2)	N=47, couple CBT, 12 weekly sessions of 75 mins. Psychoeducation, impact of provoked vulvodynia on sexuality, multifactorial view of pain, vaginal dilation exercises, cognitive restructuring, expansion of the sexual repertoire, exercises to improve pain and sexuality-relevant couple interactions, partner responses to pain, sexual motivation, and relationship intimacy	N=51, topical lidocaine treatment. 5% lidocaine ointment on the vulvar vestibule nightly for 12 weeks	FSFI, IIEF, PASS, PCS, FSDS-R	Couple CBT yielded significantly more improvements than lidocaine in pain unpleasantness (p<.001) at 6-month follow-up, pain anxiety (p<.001) and pain catastrophizing at post-treatment and 6-month follow-up, and sexual distress at post-treatment (p<.001), and resulted in better treatment satisfaction and global sexuality improvements (p<.001) at both time points. Partners significantly improved in their sexual function, sexual distress, and pain catastrophizing from pre- to post-treatment and pre-treatment to 6-month follow-up, with no significant group differences. At post-treatment and 6-month follow-up, women and partners in CBT were significantly more satisfied with their treatment than those of the lidocaine group (p=0.000).
Brotto et al 2020, Canada ²⁷	N=87, 32.3 (8.2)	N=45, CBT, 8 2.5hrs group sessions. Psychoeducation, behavioral skills training, cognitive techniques, communication skills training	N=42, MBCBT, 8.2.5 hrs group sessions. Psychoeducation provoked vulvodynia, mindfulness exercises (mindful eating, body scan, mindfulness of breath, mindfulness of sounds and thoughts, self-compassion practice). Provocation of mild (non-genital) pain in session and provoking vestibular pain at home	FFMQ, FSFI, self-report pain intensity, PCS	Those with primary provoked vulvodynia improved more in the CBT condition (p<0.01). Relationship length moderated sexual function (p<0.01). Women in shorter relationships improved more with MBCBT. Women in longer relationships improved more on sexual function with CBT.

Continues

Table 1. Continued.

Study characteristics	Sample's characteristics [total N, mean age, (SD)]	Intervention (N)	Comparison (N)	Measurements	Main results
Brotto et al 2019, Canada ²⁶	N=122, 32.35 (8.21)	N=58, 8 2-hour group CBT sessions for 8 weeks. Psychoeducation, behavioral skills training, cognitive techniques, communication skills training, and education on how provoked vulvodinia affects sexual desire, motivation, and function	N=64, MBCBT. Mindfulness exercises (mindful eating, body scan, mindfulness of breath, mindfulness of sounds and thoughts, and self-compassion practice), education on how provoked vulvodinia affects sexual desire, motivation, and function, and exposure techniques.	FSFI, FSDS-R, VAS, vulvalgesiometer for pain assessment, PCS, PVAQ, CPAQ	Between-group comparison revealed insignificant differences in pain improvement (p=0.409) and sexual function (p=0.821). 43% reported moderate or great improvement in pain (51% in the CBT group and 35% in the MBCBT group) at post-treatment and 63% at 6 months' follow-up (68% in CBT group and 58% in MBCBT group). In terms of sexual function, 43% reported moderate or great improvement at post-treatment (48% in the CBT group/38% in the MBCBT group), and, at 6 months' follow-up, 59% of participants reported moderate or great improvement (60% in the CBT group/59% in the MBCBT group).
Desrochers et al 2010, Canada ²⁹	N=69, 26.5 (6.0)	N=31, ten 90-min group sessions, 5-10 women/group. Psychoeducation, Kegel exercises, communication skills, and cognitive restructuring	N=38, topical treatment (corticosteroid analgesic cream) twice daily application, use of a water-based lubricant during intercourse	FSFI, VAS, MPQ, STAI, PASS-20, PCS, VAS, PISES	No significant differences were found between groups. Participants of the topical treatment group with higher catastrophe (p=0.04) and lower self-efficacy (p=0.01) at the start tended to have more severe pain after six months. For CBT, higher levels of baseline fear of pain and catastrophizing contributed to higher pain intensity at follow-up, whereas higher levels of pain self-efficacy were significantly associated with less pain (p=0.03).
Brown et al 2021, Canada ²⁸	N=130, 32.5 (8.3)	N=, 8 weekly 2.25-hr group CBT sessions. Psychoeducation, cessation of sexual activity, and gradual reintroduction of vaginal penetration	N=, 8 weekly MBCBT 2.25 hrs sessions. Mindfulness exercises (body scan, mindfulness of breath, self-compassion practice)	PCS, CPAQ, TIPI, ASI-3, PQICQ	No significant difference between groups was found for vaginal intercourse rates (p=0.384). MBCBT group was more likely to resume vaginal penetration if their chronic pain acceptance at pretreatment was higher (p=0.01). No time for treatment group interaction (p=0.209). For the CBT group, those with lower pretreatment pain acceptance were more likely to resume vaginal penetration (p=0.070), but this was marginally significant.

Continues

Table 1. Continued.

Study characteristics	Sample's characteristics [total N, mean age, (SD)]	Intervention (N)	Comparison (N)	Measurements	Main results
Goldfinger et al 2015, Canada ³⁰	N=20, 26.4 (8.7)	N=10, eight 1.5-hour individualized CBT sessions. Psychoeducation, reconceptualization of provoked vulvodynia as a pain condition, desensitization exercises, sexual communication skills training, and cognitive restructuring	N=10, eight 1.5-hour one-on-one physical therapy sessions (exercises, manual techniques, sEMG, progressive vaginal penetration exercises with silicone vaginal dilators)	FSFI, PCS, CSQ, MPQ	Both groups demonstrated significant decreases in vulvar pain during sexual intercourse, with 70% and 80% of participants in the CBT and physical therapy groups demonstrating a moderate clinically important decrease in pain (30%) after treatment. No differences between-group were found post-treatment. The CBT demonstrated better sexual functioning at 6-month follow-up (p=0.013).
Rosen et al 2021, Canada ³¹	N=108 (& partners), 27.0 (6.2)	Couple CBT, 12 weekly 75-minute sessions. Psychoeducation, breathing techniques, vaginal dilation exercises. cognitive restructuring, expansion of sexual repertoire	N=55, 5% lidocaine ointment on the vulvar vestibule nightly for 12 weeks	NRS, FSFI, STAI, WHYMP (partner perception of pain), couple's sexual goals (intimacy, avoidance etc.)	Sexual function was significantly improved for the CBT group post-treatment (p=0.000). The improvement was greater for those women whose partner demonstrated higher levels of anxiety (p<0.01) and for women with lower sexual goals (p=0.001).
Masheb et al 2009, USA ³³	N=47, 43.0 (12.1)	10 weekly CBT individual 60-minute sessions. Self-management skills regarding thoughts, feelings, and behaviors, coping skills, role-playing, and problem-solving.	N=25, 10 weekly individual 60-minute sessions. Supportive psychotherapy. Participants' assistance in emotional expressions, empathetic understanding, active listening	MPI, MPQ, FSFI, BDI, PASS	CBT reported significantly greater improvement in pain severity (p=.014), and improvement in sexual function (p=.034) (pre- to post-treatment). Participants in the CBT group reported significantly greater improvement and satisfaction in 1-year follow-up than participants in the supportive psychotherapy group (p<.05).

Abbreviations: CBT=Cognitive Behavioral Therapy; MBCBT=Mindfulness Based Cognitive Behavioral Therapy; MPI=Multidimensional Pain Inventory; MPQ=McGill Pain Questionnaire; FSFI=Female Sexual Function Index; IIEF= International Index of Erectile Function; BDI=Beck Depression Inventory; PASS=Pain Anxiety Symptoms Scale; PCS= Pain Catastrophizing Scale; CSQ=Coping Strategies Questionnaire; VAS= Numeric Visual Analogue Scale; STAI=State-Trait Anxiety Inventory; PVAQ=Pain and Vigilance Awareness Questionnaire; PISES=Painful Intercourse Self-Efficacy Scale; SFI= Sexual Functioning Inventory; BSI-GSI=Global Severity Index of the Brief Symptom Inventory; PVAQ=Pain Vigilance and Awareness Questionnaire; CPAQ=Chronic Pain Acceptance Questionnaire; FSDS-R=Female Sexual Distress Scale-Revised; STAI=State-Trait Anxiety Inventory; PASS-20=Pain Anxiety Symptoms Scale; MFSQ=McCoy Female Sexuality Questionnaire; HADS=Hospital Anxiety and Depression Scale; MFSQ=McCoy Female Sexuality Questionnaire; FFMQ= Five-Facet Mindfulness Questionnaire; NRS= Numeric rating scale for pain during intercourse; WHYMP= West Haven-Yale Multidimensional Pain Inventory; TIPI=Ten-Item Personality Inventory, ASI-3=Anxiety Sensitivity Index, PQICQ=Patient Global Impression of Change questionnaire

last study found no significant differences between groups. However, for CBT, higher levels of fear of pain and catastrophizing post-treatment contributed to higher pain intensity at follow-up measurements, whereas higher levels of self-efficacy regarding pain management were associated with less pain post-treatment.²⁹

One of the included studies compared CBT and physical therapy. The comparison arm implemented muscle relaxation techniques and progressive vaginal penetration exercises.³⁰ A decrease in vulvar pain during sexual intercourse was found for both groups. With respect to coping strategies, an improvement was reported for both arms pre- and post-treatment, but this was statistically significant only for the CBT group ($p < 0.001$). Sexual function did not differ significantly between pre- and post-treatment for either of the arms, but was significantly improved only for the CBT group at the 6-month follow-up assessment ($p = 0.013$).³⁰

One study implemented a 3-group comparison, by implementing psychotherapeutic (CBT), surgical (vestibulectomy), and neuromuscular rehabilitation (surface electromyographic biofeedback) interventions.²⁴ Bergeron and colleagues reported significantly reduced pain ($p < 0.01$) for all three interventions, with the greatest reduction being reported by the vestibulectomy group at post-treatment and at 6-month follow-up.²⁴ Concerning sexual function, a significant improvement was noted for all three groups ($p < 0.01$) between post-treatment and 6-month follow-up.

Quality evaluation results based on the modified Jadad Scale

The assessment of the studies' methodological assessment was conducted with the modified Jadad Scale.²² All of the included RCTs were of high quality, with an overall score between 5 and 7 (on a scale of 0–8). All studies used randomization, ensuring a high level of internal validity. Variations in the adequacy of the randomization process were noted, as some studies were not double-blinded. However, the nature of the CBT intervention constitutes double-blind protocols difficult to implement. All studies clearly described their eligibility criteria, improving sample comparability. However, only one study reported adverse events or potential side effects of the applied interventions. Lastly, most studies used appropriate statistical methods, increasing the reliability of the findings. Results of the quality evaluation are being provided as supplementary material (S1). A quantitative synthesis was conducted due to heterogeneity in interventions and outcomes.

Discussion

Vulvodynia is a chronic condition with a significant impact on sexual function, psychological well-being, and interpersonal relationships.¹⁰ Despite its high prevalence, the lack of early diagnosis and the absence of a universally accepted treatment protocol make its management difficult.³⁴ Existing pharmacological and surgical approaches often do not produce satisfactory results, leading patients to seek alternative interventions. To the authors' knowledge, this is the first systematic review investigating the effectiveness of CBT as a non-pharmacological option, focusing on its role in reducing perceived pain and improving sexual function.

Given the methodological and clinical heterogeneity of the included studies, the discussion is thematically organized based on two main axes: the type of comparator intervention (e.g., pharmaceutical, psychotherapeutic, etc.) and the delivery format of CBT (e.g., group-based, individual, or couple therapy). This subgroup-oriented structure aimed to clarify the interpretability of findings across diverse clinical contexts and intervention settings.

Concerning pharmaceutical interventions, even though the findings were slightly contradictory, the four studies that compared CBT and topical treatments underscored the superiority of CBT, particularly over time. Regarding sexual function, CBT yielded significantly better outcomes for three of them,^{24,25,31} and no significant differences post-treatment regarding pain.^{25,29,31,32} However, for two of them, the 6-month follow-up measurements revealed improvements in pain for the CBT arms.^{25,32} A plausible explanation for the lack of difference immediately post-treatment could be related to the impact of expectation and immediate response to treatment, regardless of the method.³⁵ It is known that pharmacological approaches can influence the individual's short-term experience through mechanisms such as enhancing self-confidence in symptom management and general attention to health care.³⁶ However, the maintenance of benefits over time, as seen in the results of the studies after 6 months, may reflect more stable changes achieved through CBT. As shown by literature regarding chronic pain, CBT helps individuals identify and reframe dysfunctional thoughts about pain, thereby reducing catastrophizing – a factor that often increases the subjective perception of pain.³⁷ Through techniques such as selective attention regulation and cognitive restructuring,³⁸ participants may have learned to cope with pain in more adaptive ways, reducing the stress response and passive avoidant behavior. This finding could also be ex-

amined from a neurobiological perspective. Chronic pain is associated with increased activity in brain areas involved in emotional regulation and pain processing, such as the amygdala and the prefrontal cortex.³⁹ CBT has been shown to contribute to neuroplasticity by remodeling these networks, reducing pain hypersensitivity, and enhancing emotional regulation.⁴⁰ After all, empirical and theoretical evidence substantiate the long-term efficacy of CBT, as it enables individuals to develop the skills necessary to function as their own therapist.⁴¹

Four of the included studies compared CBT with other psychotherapeutic approaches. Three of them compared CBT with MBCBT, and the comparison groups concluded with similar findings. Even though the percentages of women who reported improvements in terms of pain intensity and sexual function were greater for the CBT group,²⁶ especially for those in longer relationships,²⁷ no significant differences between groups were found for both variables.²⁶⁻²⁸ The similar effectiveness of CBT and MBCBT may be explained by the similarities in the protocols applied in the studies. Both treatments included common techniques, such as psychoeducation, relaxation exercises, and pain management strategies,²⁶⁻²⁸ which are key mechanisms of improvement for both pain intensity and sexual function.^{42,43} Also, MBCBT incorporates CBT elements,⁴⁴ probably offering similar benefits, even if the mechanisms of action differ. As far as the fourth study is concerned, this compared CBT with supportive psychotherapy.³³ Results highlighted the efficacy of CBT, with participants reporting significant improvements in pain severity as well as sexual function, with these changes being maintained even one year later. CBT directly targets the cognitive and behavioral mechanisms that maintain pain and difficulties in sexual functioning.^{45,46} Through the identification and modification of dysfunctional thoughts, exposure, and training in coping techniques, CBT offers more structured strategies compared to supportive psychotherapy. Empathy and active listening are core principles of every psychotherapeutic intervention, including CBT. Thereby, the additional targeted techniques for symptom relief may explain why participants who received CBT sessions reported better outcomes, a finding that is in line with previous research comparing the two approaches.^{8,47}

Two of the studies compared CBT with non-pharmaceutical and non-psychotherapeutic interventions, with their findings being contradictory.²⁴ One of them made a three-way comparison by examining the efficacy of vestibulectomy, sEMG biofeedback, and CBT on pain and sexual function. All three interventions resulted in significant improvements for their partic-

ipants post-treatment, and gains were maintained at 6-month follow-up for all conditions.²⁴ These results appear encouraging; however, when carefully examining the study's characteristics, interesting findings occur. For example, many participants in the vestibulectomy refused to go on with the procedure, and some of the analyses were conducted based on estimated and not collected data. In addition, there was a statistically significant dropout rate for the sEMG biofeedback group, possibly implying that the time needed to be invested in this approach and the repetitive exercises may discourage patients from complying with the protocol. The fact that the CBT group did not improve sexual function in a greater way compared to sEMG and vestibulectomy could be characterized as puzzling. This may be because improved sexual function is dependent on the degree of pain that one experiences, as at the baseline measurements, women in the CBT group reported lower pain levels and better sexual function compared to the other groups. With respect to the other study, this compared CBT with a physiotherapy protocol. Again, outcomes were significantly improved for both groups, but the important difference was at the 6-month follow-up measurement. The CBT group maintained the improvement for sexual function, complementing its effect on the overall psychological well-being, reduction in anxiety related to sexual activity, and sustained improvements in pain management.³⁰

One notable aspect of the included studies is their differentiation regarding the way CBT was delivered. In addition to the comparator type, the mode of CBT delivery (group, individual, or couple-based) was also considered as a qualitative axis for interpretation, as it may influence both therapeutic outcomes and patient engagement. Six of them applied to group CBT, whereas two of them couple CBT and two individualized sessions. Even though a direct comparison would probably be unfounded due to the different number of studies, when comparing the group and the individualized interventions, group-level interventions appeared as more efficient. They enhanced the sense of support and sharing of experiences, while individual sessions provided more targeted intervention on individual problems. Desrochers et al. reported that individual CBT sessions showed slightly better results in pain management and reductions.²⁹ In contrast, Brotto et al. demonstrated that group CBT sessions were beneficial, particularly for women in long-term relationships, highlighting that group dynamics can act as an additional factor enhancing therapeutic outcomes. Concerning the couple's CBT, the interesting finding lies in the fact that the partner's perceptions affected the outcomes regarding pain and sexual

function,³¹ and when the woman improved in terms of pain and sexual function, so did the partner's pain catastrophizing and sexual anxiety and function.³² This finding confirms results from a pilot study highlighting that, following CBT, partners reduced pain catastrophizing.⁴⁸ The fact that partner pain catastrophizing contributes to women's pain in vulvodynia samples and that partners also endure sexual difficulties due to the diagnosis emphasizes the importance of the relationship's intimacy, underlining how the perception and management of pain by the partner can directly affect the other's experience.

The present review demonstrates specific strengths, such as adherence to the PRISMA guidelines, inclusion of only RCTs, and thorough assessment of the studies' methodological quality. To further clarify the interpretability and practical relevance of our findings, the following two sections discuss key methodological limitations of the included studies, followed by the clinical implications and potential applications of CBT in vulvodynia management.

Despite its strengths, this review bears certain limitations that must be acknowledged. The first concerns the heterogeneity of CBT protocols; some focused on restructuring dysfunctional thoughts and pain management, while others included self-efficacy training or communication skills. In addition, the comparator interventions varied widely (e.g., medication, physical therapy, surgery), making direct comparisons more complex. There was also an inconsistency in outcome measures; most were based on self-report, with only one study using an objective tool for pain measurement. An additional methodological issue that arises concerns the absence of sample size calculation (power analysis) in several of the included studies. This omission limits the internal validity of their results, as the adequacy of the sample to detect statistically significant differences is not ensured. Furthermore, it makes it difficult to draw firm conclusions and reduces the generalizability of the review findings.⁴⁹ Although the available data did not allow the conduction of a meta-analysis and thus a formal quantitative assessment of publication bias (e.g., funnel plot, Egger's test) was not feasible, the possibility of publication bi-

as remains a notable limitation of the present review. To minimize this risk, a comprehensive search strategy was employed across multiple databases, along with a backward reference search of included studies. Nonetheless, it is possible that unpublished trials or studies with non-significant results were omitted, which could have affected the completeness and objectivity of the findings.

From a clinical standpoint, CBT emerges as a promising non-pharmacological treatment for vulvodynia. Considering the high rates of misdiagnosis or delayed diagnosis, clinician education —particularly among gynecologists— is crucial. Additionally, couple-based CBT appears especially beneficial, not only for improving individual outcomes but also for addressing dyadic dynamics that influence pain perception and sexual satisfaction. Findings from a couple of interventions highlight the importance of partner involvement in the therapeutic process, as changes in their attitudes and perceptions directly affect the woman's pain experience and sexual functioning. Future interventions could systematically incorporate the partner to jointly manage the problem, enhancing empathy and preventing catastrophe on both sides. Assessing the quality of the relationship, sexual communication, and the partner's beliefs about pain can guide individualized interventions and improve the overall effectiveness of treatment.

In summary, CBT appears to be an effective non-pharmacological intervention for reducing pain and improving sexual function in women with vulvodynia. Despite heterogeneity in study designs and outcome measures, the findings indicate promising and sustained benefits, particularly when interventions are tailored to individual or couple dynamics. Future research with standardized methodologies and partner-inclusive approaches may further strengthen the evidence base and inform clinical practice.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: <https://doi.org/10.22365/jpsych.2025.013>

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Ανασκόπηση

Συστηματική ανασκόπηση της αποτελεσματικότητας της Γνωσιακής Συμπεριφορικής Θεραπείας για τον πόνο και τη σεξουαλική λειτουργία στην αιδοιοδυνία

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ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 20 Φεβρουαρίου 2025/Αναθεωρήθηκε 9 Ιουνίου 2025/Δημοσιεύθηκε Διαδικτυακά 5 Αυγούστου 2025

ΠΕΡΙΛΗΨΗ

Η αιδοιοδυνία αποτελεί ένα υποδιαγνωσμένο σύνδρομο πόνου με επίμονη διάρκεια συνήθως χωρίς αναγνωρίσιμη οργανική αιτία. Επηρεάζει αρνητικά την ποιότητα ζωής, την ψυχική υγεία, τις ρομαντικές σχέσεις και τη σεξουαλική λειτουργικότητα των γυναικών. Σκοπός της παρούσας ανασκόπησης ήταν η συστηματική προσέγγιση των ερευνητικών δεδομένων που έχουν προκύψει από τυχαίοποιημένες κλινικές δοκιμές σχετικά με την αποτελεσματικότητα της Γνωσιακής Συμπεριφορικής Θεραπείας στον αντιλαμβανόμενο πόνο και τη σεξουαλική λειτουργικότητα γυναικών με αιδοιοδυνία, ασχέτως χρονικής στιγμής δημοσίευσης. Η ανασκόπηση πραγματοποιήθηκε σύμφωνα με τις κατευθυντήριες οδηγίες PRISMA. Η αναζήτηση της βιβλιογραφίας πραγματοποιήθηκε βάσει συγκεκριμένων κριτηρίων καταλληλότητας στις βάσεις δεδομένων Pubmed, PsycInfo και Scopus με τη χρήση των κατάλληλων λέξεων-κλειδιά. Η μεθοδολογική ποιότητα των συμπεριλαμβανομένων μελετών αξιολογήθηκε με το Jadad Scale. Η αναζήτηση κατέληξε σε 10 μελέτες που συνέκριναν την αποτελεσματικότητα της Γνωσιακής Συμπεριφορικής Θεραπείας εν συγκρίσει με άλλες ψυχοθεραπευτικές προσεγγίσεις και κλινικές, φαρμακευτικές και χειρουργικές παρεμβάσεις σε 835 γυναίκες με αιδοιοδυνία. Τα αποτελέσματα ανάδειξαν την υπεροχή της Γνωσιακής Συμπεριφορικής Θεραπείας σε σχέση με τοπικές φαρμακευτικές θεραπείες με σημαντικές βελτιώσεις στη σεξουαλική λειτουργία και τη διαχείριση του πόνου, κυρίως σε βάθος χρόνου. Οι συγκρίσεις με άλλες ψυχοθεραπευτικές προσεγγίσεις (γνωσιακή θεραπεία βασισμένη στην ενσυνειδητότητα, υποστηρικτική ψυχοθεραπεία) κατέληξαν σε παρόμοια αποτελέσματα. Εν συγκρίσει με φυσικοθεραπευτικά και χειρουργικά πρωτόκολλα, η Γνωσιακή Συμπεριφορική Θεραπεία κατέληξε σε ευνοϊκότερα αποτελέσματα, αν και η βελτίωση της σεξουαλικής λειτουργίας ήταν σημαντική κυρίως κατά την παρακολούθηση 6 μήνες μετά την ολοκλήρωση των παρεμβάσεων. Η Γνωσιακή Συμπεριφορική Θεραπεία φάνηκε να βοηθά μέσω της αμφισβήτησης δυσλειτουργικών σκέψεων, της μείωσης της καταστροφολογικής ερμηνείας γύρω από τον πόνο, και την ανάπτυξη εναλλακτικών στρατηγικών αντιμετώπισής του. Παρά τις ενθαρρυντικές ενδείξεις, υπήρχαν διαφοροποιήσεις σε επίπεδο γνωσιακών-συμπεριφορικών παρεμβάσεων, των ομάδων σύγκρισης και των εργαλείων αξιολόγησης των υπό διερεύνηση μεταβλητών, γεγονός που καθιστά δύσκολη την άμεση σύγκριση των ευρημάτων. Τα αποτελέσματα, τα οποία παρουσιάζονται αφηγηματικά βάσει τύπου παρέμβασης και ευρημάτων, ανάδειξαν τη Γνωσιακή Συμπεριφορική Θεραπεία ως μια υποσχόμενη, μη φαρμακευτική προσέγγιση για τη διαχείριση της αιδοιοδυνίας. Η εκπαίδευση των κλινικών γιατρών και των ψυχοθεραπευτών θα συμβάλει στην ενίσχυση της έγκαιρης διάγνωσης και την αποτελεσματική θεραπεία αυτής της διάγνωσης.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Αιδοιοδυνία, γνωσιακή συμπεριφορική θεραπεία, πόνος, σεξουαλική λειτουργία, τυχαίοποιημένη κλινική δοκιμή, συστηματική ανασκόπηση.

Review

Timing and self distortions in psychosis: Is it an insula matter?

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ARTICLE HISTORY: Received 29 January 2025/Revised 10 July 2025/Published Online 20 December 2025

ABSTRACT

The concept of timing is an interesting way to understand how the body and brain construct the concept of self, but also how self-distortions arise in the case of psychosis. Analysis of temporal representations in psychosis highlights a deficit that includes both the subjective experience of the flow of time, i.e., time perception, and the ability to process temporal information inherent to any perceptual event, i.e., perceptual timing. The representation of the self is stabilized within temporal windows, and thus the self is experienced as continuous in time. Disturbance in the sense of time, in the form of a loss of temporal continuity, has been described by phenomenologists as a central subjective experience of schizophrenia. The positive symptoms of schizophrenia are associated with overestimation of interval timing, i.e., an acceleration of the 'internal clock', while dopamine neurotransmission is likely to regulate the speed of the internal clock. Moreover, findings highlight the importance of interoceptive precision as an aspect of time perception, since accuracy in time perception is related to interoceptive accuracy and vagal activity. Insula contributes significantly to the total awareness of reality. Global emotional moments and meta-representations of the conscious self are created in the anterior insula. In psychosis, the interaction between the default-mode network and the frontoparietal executive network is disrupted by aberrant salience signals from the right anterior insula. Here, we describe the role of the insula as a key hub for the recognition of major aspects of the self, in parallel with the role of interoceptive predictive coding, which reflects the contribution of the insula to the temporality of the self. Based on the above, new insights focus on the development and implementation of rehabilitation strategies that specifically target the temporal deficits observed in psychosis. New therapeutic interventions are based on sensory education and enhancing the multisensory integration of these patients.

KEYWORDS: Time, temporality, self, psychosis, interoceptive, insula, salience network.

Timing representation

Time is intuitively understood. High alertness, novel events, and focused cognitive activity are associated with an underestimation of time. Conversely, unpleasant situations, fatigue, and drowsiness are associated with an extension of subjective time. The emotional quality of the experience also seems to influence the subjective sense of time.¹ The ability to perceive time, to predict events, and to process temporal patterns is a

major function of the brain. Sensory perception, motor control, cognition, and consciousness require reliable time perception, which needs the presence of a highly accurate endogenous time calculation system.²

Analysis of temporal representations highlights differentiations at the perceptual level that include both the subjective experience of the flow of time (i.e., the perception of time) and the ability to process temporal information inherent in any perceptual event (i.e.,

perceptual timing). From a phenomenological perspective, the distinction between these two concepts coincides with the distinction between structure and content. Moreover, both perceptual timing and perception of time can be explored either explicitly or implicitly. Explicit processing involves explicit judgments about the temporal properties of external stimuli, such as duration, order, or simultaneity. In contrast, implicit processing is automatically engaged whenever sensorimotor information has a temporal structure, even without receiving specific instructions to focus on time.³ In table 1 are described the time parameters, the relative experiments, and the brain structures involved.

Time perception appears to be the result of the activity of a neural network rather than a single brain region. The temporal processing of various neural circuits depends on the activation of different brain regions, which allows rapid adaptations of the organism to the temporal characteristics of the environment.⁸ The role of the dorsolateral prefrontal cortex, the supplementary motor area, and the right inferior frontal cortex is highlighted.⁹ Other brain regions involved in time perception are the cerebellum, the left inferior insula, the left putamen, and the hippocampus.¹⁰ Time processing appears to be carried out in different regions or networks, depending on different time durations, with the cerebellar-thalamo-cortical network being mainly involved in time intervals shorter than a second, while the corticostriatal networks are involved in time intervals from a second to a minute.¹¹

Time perception also involves brain areas important for motor behavior. Damage to areas such as the cere-

bellum and basal ganglia, therefore, affects movement and time perception, suggesting that spatial and temporal processes work together to shape precise actions, thoughts, or emotions in specific time windows. Several neurotransmitter systems are involved in this function, especially dopamine.¹² Dopamine signaling is involved in biological rhythms, particularly in relation to feeding, reward, and activity, while time perception and reward processing interact via a common dopaminergic mechanism.¹³ Dopamine antagonists, such as antipsychotics, reduce the internal clock speed, while dopamine agonists, such as amphetamine, cocaine, or cannabis, increase it.¹⁴

Timing distortions in psychosis

Research on perceptual timing and the perception of time suggests that an impairment in the temporal aspects of early perceptual processing may constitute a critical substrate of psychotic functioning.³ Based on this reasoning, the core symptoms of schizophrenia can be considered as manifestations of a globally disrupted time processing.¹⁵ Therefore, there may be a common mechanism underlying these timing dimensions, which may contribute to the pathophysiology of patients with schizophrenia.¹⁶ Temporal precision, i.e., consistency in perception, is clearly deficient in patients with schizophrenia, suggesting that patients' explicit and implicit judgments of time are significantly more variable, compared to healthy controls. Psychotic patients have deficits in the explicit detection of rhythm irregularities and in the estimation of durations, ranging from milliseconds to several minutes, in a wide range of tasks, includ-

Table 1. The concepts of Timing - experimental paradigms

Perceptual timing: The temporal resolution in processing events - The ability to process temporal information inherent in any perceptual event - Phenomenologically, it represents the content ¹
Time perception: The subjective experience of the flow of time - The subjective experience of the passage of time and of events' duration - Phenomenologically, it represents the structure ³
Explicit processing of time: Involves explicit judgments about the temporal properties of external stimuli, such as duration, order, or simultaneity - Activation: basal ganglia, with co-activation of the supplementary motor area, inferior frontal cortex and cerebellum.
Implicit processing of time: automatically engaged whenever sensorimotor information has a temporal structure, even without receiving specific instructions to focus on time - Activation: left lateral prefrontal and inferior parietal cortex ³
Explicit investigation of perceptual timing: Evaluating the simultaneity vs. asynchrony of two stimuli, the specific question "are these stimuli simultaneous?" makes it explicit, while the possibility to estimate the timeframe within which multiple stimuli are highly likely to be perceived explores timing of perception ⁴
Explicit investigation of perception of time: In duration discrimination tasks, the participant is asked to decide which interval is longer, where two time intervals are presented in sequence ⁵
Implicit investigation of Perceptual timing: In the double-flash illusion task, the instructions are for the number of perceived flashes, which indirectly gives information about the temporal resolution. Participants are asked how many flashes they perceive, and the illusion occurs when one flash, simultaneously accompanied by two beeps is erroneously perceived as two flashes. An enlarged temporal integration window for audio-visual stimuli was found in schizophrenia patients ⁶
Implicit investigation of perception of time: Participants implicitly use temporal information inherent to the speed of moving sensory stimuli to predict their eventual locations, evaluating, for example, whether moving stimuli will collide ⁷

ing both verbal and motor responses, affecting different sensory functions. They also have problems using implicit temporal cues to predict the appearance of targets during an attentional orienting task.¹⁷

Abnormalities in what we refer to as ‘perceptual timing’ have been proposed as a core deficit in the prodromal phase of schizophrenia. For example, a longer temporal binding window is associated with symptoms of disorganization, with the severity of hallucinations, and with higher levels of schizotypy in subclinical populations.^{18,19} Perceptual timing is critical for multisensory integration, the ability of humans to combine different sensory information from the same perceptual event into a single mental representation. The ability and intensity of multisensory integration depend on the characteristics of low-level physical stimuli, such as their timing (e.g., a pair of stimuli is more likely to be integrated if they are close in time). Research has shown that schizophrenia is characterized by distinct alterations in multisensory processing.²⁰ The ability to integrate sensory information has been linked to the emergence of a sense of self,²¹ while a link has been found between multisensory dissociation and self-perception disorders.²² For example, the integration of sensory information that is usually perceived as independent can cause sensory overload, alterations in sensory filters, and unclear perceived identity, causing a feeling that the individual lives in a disjointed world, a symptomatology reminiscent of what is observed at a phenomenological level in patients with schizophrenia.²³

Positive symptoms of schizophrenia may be associated with distortions in time perception. A meta-analysis showed that positive symptoms of schizophrenia are associated with overestimation of interval timing, i.e., acceleration of the internal clock.²⁴ The findings are consistent with the view that accelerated time perception is associated with hypervigilance, which may underline the generation of positive symptoms. This suggests that the deficit in time perception may be an endophenotype of schizophrenia.²⁵ Another meta-analysis showed that time perception in schizophrenia can be shorter or longer, compared to objective time, suggesting a heterogeneous internal clock in patients with schizophrenia.⁸ Similar disturbances in time processing have also been found in individuals with high schizotypy scores or in the prodromal syndrome of schizophrenia, which may be a specific vulnerability feature.²⁶ Finally, individuals at high risk for psychosis had poorer temporal accuracy, compared to controls, while the degree of temporal inaccuracy was associated with abnormal connectivity in cerebellar circuitry.²⁷

Timing and self fragmentation in psychosis

The different views on the concept of self (table 2) include, to a greater or lesser extent, the concept of time. Difficulties in integrating sensory information over time may affect the self, due to their impact on the ability to create unified representations, which lead to an uninterrupted flow of sensory inputs. Impairment in perceptual timing may also be

Table 2. The various concepts of Self.

- The self as “Me”, corresponding to the self as an object of experience (I see «Me» in the future), and the self as “I”, reflecting the self as a subject of experience («I» see Me in the future) (James, Wittgenstein)^{28,29}
- The ‘Me’ is the organized set of attitudes of others that an individual adopts, and the ‘I’ is an individual’s response to the attitudes of others (Mead)³⁰
- Self-awareness depends on social mirrors, “what is not public is not conscious” (Whitehead)³¹
- There is the ‘private self’, which includes the individual’s knowledge of his or her own characteristics or behaviors, the ‘public self’, which relates to general human self-awareness, and the ‘collective self’, which relates to collective views of the self (Triandis)³²
- Distinctions between ecological, interpersonal, extended, private, and conceptual aspects of the self (Neisser)³³
- The “who” (self) system contains the other-as-self mechanism (to perceive other people egocentrically as proxies of the self, as occurs through the processes of mentalizing and empathizing), and the self-as-other mechanism (to overtly depict other people during acts of communication (Brown)³⁴
- The Self-Concept is made up of autobiographical knowledge and relies on all the attributes, traits, beliefs, values, social status, roles, and physical characteristics we attribute to ourselves (Prebble)³⁵
- The Subjective Sense of Self (“the I-self”, as initially proposed by James), is made up of two hierarchically related forms of present-moment conscious self-experience: irreflective self-experience (what some philosophers call “Qualia”, and self-awareness (Prebble)³⁵
- The Subjective Sense of Self corresponds to both a “minimal embodied self” and a “minimal experiential self”. The first one includes core biological and ecological aspects, which allow the system to distinguish between the self and the non-self. The second one contributes to an embodied sense of ownership (i.e., confers the feeling that I am the one undergoing the experience) and a sense of agency (i.e., confers the feeling that I am the one who is initiating or causing an action) (Gallagher)³⁶
- In the context of Chinese Buddhist culture, the theory of self is related to transforming the self into non-self, through discipline and meditation (Wang)³⁷

responsible for the altered sense of temporal continuity described at a phenomenological level for psychosis. Disturbance in the sense of time, in the form of the loss of the simple continuity of past, present, and future, has been described by phenomenologists as a central subjective experience of psychosis.^{38,39} Modelling intentionality in the human brain⁴⁰ also suggests a persistent failure of intentionality in psychotics, due to the inappropriateness of an intentional object or due to the absence of an intentional object altogether.⁴¹

Fragmentation of the experience of time, in the form of discontinuity, *déjà vu/vecu*, etc., characterizes the so-called 'anomalous time experience' in psychosis. At the phenomenological level, patients with schizophrenia report a loss of continuity in the sense of time, temporal fragmentation of self-experience, and usually feel that time is running slower or faster.⁴² Abnormal temporal experience has been considered a key aspect of 'self-disorder', a key phenomenological feature of schizophrenia that suggests a structural instability of the first-person perspective. Time, indeed, is a dynamic component of consciousness, and phenomenological philosophy has interpreted the concept of time as a basic structure of the human self. Thomas Fuchs¹⁵ reviewed the phenomenological perspective on time in psychosis and concluded that core schizophrenic symptoms, such as thought disorder, thought intrusion, auditory hallucinations, and experiences of passivity, can be described as disturbances in the transcendental constitution of internal time consciousness or the microstructure of temporality.

Psychotic patients implicitly discriminate stimuli over time, just like controls, but unlike controls, they process stimuli individually and in sequence.⁴³ This finding has been interpreted as evidence of disturbed predictive coding in schizophrenia, resulting in a reduced ability to predict new events, even though attention remains on current events. This leads to fragmentation in information processing, which affects the sense of temporal continuity. It is as if the sense of self requires the experience of sensory information as continuous in time, and in turn, the sense of temporal continuity (continuous in time), relies on the ability to retain the most recent past information and predict upcoming events.⁴⁴ In the case of psychosis, inappropriate corollary discharge signals flood the allocentric system, which is overwhelmed by noisy and unpredictable information. The enhanced intentionality bias, combined with the lack of a sense of agency, causes hallucinations, reinforced in parallel with inappropriate judgments of agency.⁴⁵

Insula and sense of self

At least three distinct neural functions of self-reference have been described by neuroscientists:

a. The present-moment self-reference function (experiential focus), which is associated with the central executive network, and is composed of the dorsolateral prefrontal cortex and the posterior parietal cortex.

b. The subjective experience-related self-reference function (narrative focus) is associated with the Default Mode Network, which consists of an integrated system of autobiographical, egocentric, and social cognitive functions characterized by reflective, often non-conscious self-referential narrative thinking linking subjective experience to time, which produces one's sense of self or identity. It includes the posterior cingulate cortex, which is associated with autobiographical memory and self-referential processes, the ventromedial prefrontal cortex, which is associated with social-cognitive processes about self and others, the medial temporal lobe, which is associated with episodic memory, and the angular gyrus, which is involved in semantic processing.

c. The salience network, which acts as a 'switch', switches between activation/deactivation of the central executive network and the default mode network, depending on the degree of mental engagement. The anterior insula and the anterior cingulate cortex are involved in this. The insula has also been described as the central locus of automatic, emotional, and cognitive integration and is associated with a wide range of stimuli, including cognitive, socio-emotional, olfactory-gustatory, and interoceptive sensations, as well as the processing of pain. Therefore, the insula is a neural factor that contributes significantly to the total awareness of reality. It appears to act by tuning the mind from a state of self-referentiality of the senses to a state of complete and present-centered awareness.⁴⁶

This triple network dysfunction theory of schizophrenia postulates that the interaction between the default-mode and the frontoparietal executive network is disrupted by aberrant salience signals from the right anterior insula.⁴⁷ Anterior insular cortex is also rich in Von Economo neurons (VENs), large projection neurons which are circumstantially associated with self-consciousness and complex social emotions. In the Seth-Critchley model,⁴⁸ fast VEN-mediated connections may enable the rapid registration of visceromotor and viscerosensory signals needed for efficient updating of generative models underlying interoceptive predictive coding. Insular dysfunction appears to be one of the biological substrates of body perception disorders in schiz-

izophrenia, as well as of the alteration of the sense of self, which is characteristic of this psychiatric pathology.⁴⁹

Insula and sense of time

The brain is an inherently temporal organ because, in many ways, its main function is to learn from the past to better predict the future. Interoceptive inference remains influential in understanding predictive processing, since it brings closer the phenomenology of consciousness with that of emotionality, while intentionality seems to have essential relations with both consciousness and evolutionary selected functions.⁵⁰ It is argued that somatic-physiological changes provide the basic material for the sense of time. According to Craig (2009),⁵¹ somatic signals transmitted through the sensory pathways of the autonomic nervous system to the dorsal posterior insula provide the basis for the experience of time and for the sense of the physiological state of the body. This sense of the physiological state of the body is known as "interoception". Somatic signals are processed in the posterior-anterior pathway of the insula, integrating inputs from other areas of the brain, such as information from homeostatic, environmental, hedonic, motor, social, and cognitive data. Ultimately, global emotional moments and meta-representations of the conscious self are created in the anterior cerebral cortex of the insula. The accumulation of these emotional moments constitutes a subjective sense of time. In line with this theory, Wittmann et al⁵² found that neural activity in the posterior insula increased linearly during the encoding of a temporal stimulus. This accumulation-like neural activity may indicate the use of somatic signals to encode temporal duration. Underestimations in interoceptive time perception have been connected to different psychological conditions characterized by a diminished processing of high salience stimuli from the body.⁵³

Recently, Hashiguchi et al⁵⁴ found that activity in the right anterior insula was positively correlated with temporal duration discrimination accuracy. Teghil et al⁵⁵ conducted a meta-analytic review of neuroimaging studies to identify the neural substrates of two types of timing processing: (a) Internally based processing, which produces the main temporal representations, relying on the endogenous timing mechanism independently of the sensory environments, and (b) Externally cued processing, which detects the temporal structure of the sensory environment and integrates it with the result of internal processing to construct temporal representations. They found evidence for a partial distinction between these timing processes. The insular cortex was found to be activated during

internal processing, but more strongly during external processing. Therefore, internal processing may correspond to the use of somatic signals to encode duration, while external processing may reflect the integration of inputs from various brain regions with the main representation of internal processing.

It has been proposed that accuracy in time perception is related to interoceptive accuracy and vagal activity. Uruguchi et al⁵⁶ investigated time perception in the sub-second range and found a positive relationship between interoceptive accuracy and temporal accuracy. They hypothesized that the degree of temporal accuracy may be related to the signal-to-noise ratio, or internal noise, in the body, which may also be related to interoceptive accuracy. Examining temporal precision in relation to interoceptive precision and interoceptive sensitivity, they concluded that temporal precision is also related to vagal nerve activity. Overall, the findings highlight the importance of interoceptive precision as an aspect of time perception, which future studies can now further examine in relation to vagal nerve activity.

Perspectives

A vast literature supports the involvement of the insula in psychosis,⁵⁷ but also in anorectic behavior,⁵⁸ addictive behavior,⁵⁹ alexithymia,⁶⁰ and anosognosia.⁶¹ In figure 1 is described a scenario of timing and self-distortions in patients with psychosis is described, with the insula being a key domain of this process. Fermin et al⁶² proposed the Insula Hierarchical Modular Adaptive Interoception Control (IMAC) model, suggesting that insula modules (granular, dysgranular, and agranular), forming parallel networks with the prefrontal cortex and striatum, are specialized to form higher-order interoceptive representations. Recently, Jiang et al,⁶³ using epicenter mapping on cross-sectional magnetic resonance imaging from 1,124 individuals with schizophrenia, identified that the fronto-insular cortex (a region in the ventral part of the anterior insular cortex, characterized by the unique population of von Economo neurons) may be a major epicenter of neuro-anatomical pathophysiology in schizophrenia.

On the other hand, psychosis contains a significant autoimmune component.^{64,65} Several lines of evidence suggest a predisposition to a pro-inflammatory state in the brain in psychosis, while anti-inflammatory drugs could potentially counteract this predisposition.⁶⁶ Reviewing the clinical and pathophysiological similarities between dysmyelinating diseases and psychosis, we suggested disconnection syndrome of psychosis represents the phenomenological and behavioral outcome of a multifaceted dysmyelinating disorder,

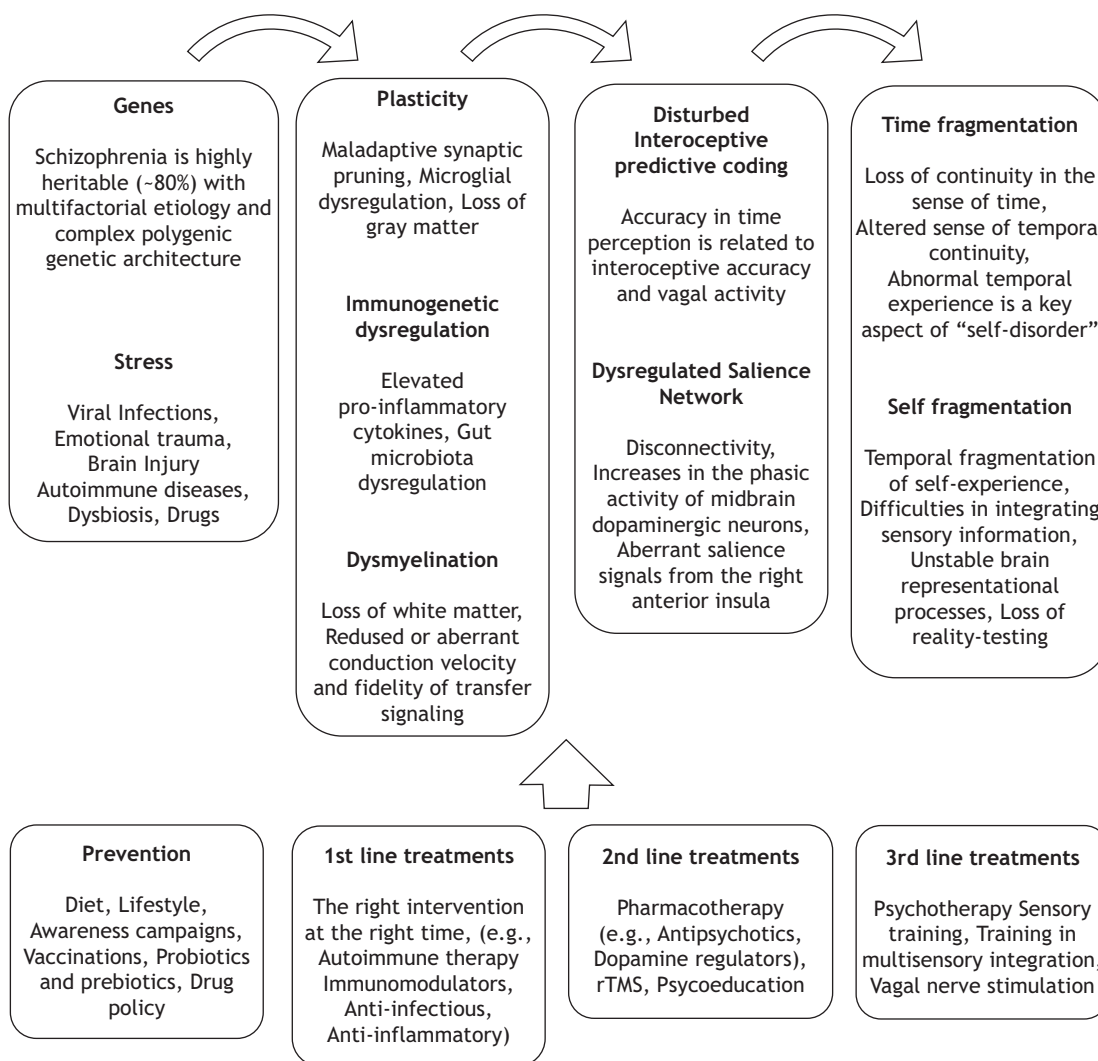


Figure 1. A scenario of distortions of timing and self, in patients with psychosis is depicted, with the insula being a key domain in this process. Therapeutic treatment follows the presumed progression of the disease over time.

based on a lifelong process of immunogenetic dysregulation.⁶⁷ Moreover, research has intensified our understanding of immunoeception and immunograms, focusing on their manifestation in a specific brain region, the insular cortex.^{68,69} Recent data revealed that immune-related information under peripheral inflammatory conditions, termed as "immunogram", was represented in specific neuronal ensembles in the insular cortex.⁷⁰

Finally, new insights focus on the development and implementation of rehabilitation strategies that specifically target the temporal deficits observed in schizophrenia. In table 3, the therapeutic interventions proposed so far in patients with psychosis are described, based on sensory training and training in multisensory integration. Integrating these strategies into the treatment of schizophrenia offers a promising direction for the improvement of temporal dysfunctions, as well as

the general rehabilitation of individuals with this disorder.³

Psychiatry must be constantly updated and apply the valuable knowledge of neuroscience, at a research, diagnostic, and therapeutic level, while psychiatrists have the obligation to apply neuroscience knowledge to clinical practice in the real world.⁷⁸ Extending, we note the concept of 'timing' is a necessary component, not only for a well-adjusted self, but also for well-designed and prioritized therapeutic interventions, in medicine,⁷⁹ psychiatry^{80,81} and psychotherapy.⁸²

In conclusion, the concept of timing is an interesting way to understand how the body and brain construct the concept of self, but also how self distortions arise, as happens in the case of psychosis. Here, we describe the role of the insula as a key hub for the recognition of major aspects of the self, in parallel with the role

Table 3. Sensory therapeutic training, as temporal recalibration, in psychotic patients.

- Mindful awareness in body-oriented therapy develops the distinct interoceptive awareness capacities of identifying, accessing, and appraising internal bodily signals that are identified in physiological models as the critical components of interoception for emotion regulation⁷¹
- Body psychotherapy is beneficial for a wide spectrum of psychic suffering. (A total of 2,180 references were screened, of which 113 studies were scrutinized and 18 RCTs finally included)⁷²
- Positive effect of dance movement therapy,⁷³ group body psychotherapy,⁷⁴ and body-oriented psychological therapy,⁷⁵ on negative symptoms in schizophrenia (multicenter randomized controlled trials).
- Dance/movement therapy is a holistic approach to diminish health discrepancies and promote wellness for people with schizophrenia⁷⁶
- Music therapy seems to help people with schizophrenia (18 RCTs studies with a total 1215 participants that compared music therapy with standard care, placebo therapy, or no treatment)⁷⁷

of interoceptive predictive coding, which reflects the contribution of the insula to the temporality of the self. Many studies show that under- or over-activation at various points along this long neural pathway leads to mental disorders, including psychosis. Bringing this

issue to the forefront, the rapidly developing fields of genetics, neuroimaging, and immunology, now aided by artificial intelligence applications,⁸³ are expected to further accelerate the diagnosis and treatment of this devastating disorder.

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Ανασκόπηση

Παραμορφώσεις χρόνου και εαυτού στην ψύχωση: Μήπως είναι θέμα της νήσου;

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ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 29 Ιανουαρίου 2025/Αναθεωρήθηκε 10 Ιουλίου 2025/Δημοσιεύθηκε Διαδικτυακά 20 Δεκεμβρίου 2025

ΠΕΡΙΛΗΨΗ

Η έννοια του χρόνου είναι ένας ενδιαφέρων τόπος για να κατανοήσουμε πώς το σώμα και ο εγκέφαλος κατασκευάζουν την έννοια του εαυτού, αλλά και πώς προκύπτουν οι παραμορφώσεις του εαυτού στην περίπτωση της ψύχωσης. Επίσης, η ανάλυση των χρονικών αναπαραστάσεων στην ψύχωση αναδεικνύει ένα έλλειμμα που περιλαμβάνει τόσο την υποκειμενική εμπειρία της ροής του χρόνου, δηλαδή την αντίληψη του χρόνου, όσο και την ικανότητα επεξεργασίας χρονικών πληροφοριών, που είναι εγγενείς σε οποιοδήποτε αντιληπτικό γεγονός, δηλαδή τον αντιληπτικό χρονισμό. Η αναπαράσταση του εαυτού σταθεροποιείται εντός χρονικών παραθύρων και έτσι ο εαυτός βιώνεται ως συνεχής στον χρόνο. Η διαταραχή στην έννοια του χρόνου, με τη μορφή απώλειας της χρονικής συνέχειας, έχει περιγραφεί από τους φαινομενολόγους ως κεντρική υποκειμενική εμπειρία της σχιζοφρένειας. Τα θετικά συμπτώματα της σχιζοφρένειας σχετίζονται με υπερεκτίμηση του χρονισμού των διαστημάτων, δηλαδή μια επιτάχυνση του «εσωτερικού ρολογιού», ενώ η ντοπαμίνη ρυθμίζει πιθανόν την ταχύτητα αυτού. Επιπλέον, τα ευρήματα υπογραμμίζουν τη σημασία της ενδοδεκτικής ακρίβειας, ως πτυχή της αντίληψης του χρόνου, καθώς και την εγκυρότητα αντίληψης του χρόνου, που σχετίζεται με την ενδοδεκτική ακρίβεια και την πνευμονογαστρική δραστηριότητα. Η νήσος του Reil συμβάλλει σημαντικά στην πλήρη επίγνωση της πραγματικότητας. Στην πρόσθια νήσο δημιουργούνται οι συνολικές συναισθηματικές στιγμές και μετα-αναπαραστάσεις του συνειδητού εαυτού. Στην ψύχωση, η αλληλεπίδραση μεταξύ του δικτύου προεπιλεγμένης λειτουργίας και του μετωποβρεγματικού εκτελεστικού δικτύου διαταράσσεται από την ανώμαλη σηματοδότηση της δεξιάς πρόσθιας νήσου. Εδώ περιγράφουμε τον ρόλο της νήσου του Reil, ως βασικό νευρωνικό κόμβο για την αναγνώριση σημαντικών πτυχών του εαυτού, παράλληλα με τον ρόλο της ενδοδεκτικής προγνωστικής κωδικοποίησης, η οποία αντανάκλα τη συμβολή της νήσου στη χρονικότητα του εαυτού. Με βάση τα παραπάνω, νέες πρακτικές εστιάζουν στην ανάπτυξη και εφαρμογή στρατηγικών αποκατάστασης που στοχεύουν ειδικά στα χρονικά ελλείμματα που παρατηρούνται στην ψύχωση. Οι θεραπευτικές παρεμβάσεις βασίζονται στην αισθητηριακή εκπαίδευση και την ενίσχυση της πολυαισθητηριακής ολοκλήρωσης των ασθενών.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Χρόνος, χρονισμός, εαυτός, ψύχωση, νήσος, ενδοδεκτικό σύστημα, σύστημα διακριτότητας.

Review

Towards Precision ECT: A systematic review of epigenetic biomarkers in treatment-resistant depression

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ARTICLE HISTORY: Received 24 April 2025/Revised 19 July 2025/Published Online 5 August 2025

ABSTRACT

Electroconvulsive therapy (ECT) remains one of the most effective treatments for patients with treatment-resistant major depressive disorder (TR-MDD). However, the biological mechanisms underlying its therapeutic effects are not yet fully understood. Epigenetic regulation has recently emerged as a promising field for elucidating the molecular underpinnings of ECT response. This systematic review aimed to identify and synthesize existing studies investigating epigenetic biomarkers associated with ECT outcomes in human populations. A systematic review was conducted in PubMed and Scopus for studies published between January 2015 and March 2025. The review adhered to PRISMA 2020 guidelines. Inclusion criteria were: (1) original, peer-reviewed studies; (2) investigation of ECT-induced effects on epigenetic markers; and (3) diagnosis of major depressive disorder. Extracted data included epigenetic targets, patient characteristics, ECT parameters, and clinical outcomes. Risks of bias and heterogeneity were taken into account in the synthesis. Eleven studies met the inclusion criteria, encompassing a total of 498 patients with TR-MDD. Across studies, 31 promising epigenetic biomarkers were identified, including genes involved in neuroplasticity, hypothalamic–pituitary–adrenal (HPA) axis regulation, inflammation, immune signaling, and non-coding RNAs. DNA methylation and microRNA (miRNA) expression were the most frequently studied mechanisms. No studies to date have investigated histone modifications in human subjects undergoing ECT. This systematic review provides preliminary evidence that epigenetic mechanisms—particularly DNA methylation and miRNA expression—may play a role in modulating response to ECT in patients with TR-MDD. While these findings offer important insights for clinical stratification and precision psychiatry, they are limited by small sample sizes and methodological variability. Larger, standardized, and longitudinal studies are needed to validate these initial findings and support translational applications.

KEYWORDS: Electroconvulsive therapy, treatment-resistant depression, epigenetics, biomarkers, precision psychiatry.

Introduction

Electroconvulsive Therapy (ECT) is a noninvasive brain stimulation involving controlled induction of generalized seizures under anesthesia and muscle relaxation.¹ It has demonstrated robust and consistent efficacy in the treatment of severe and treatment-re-

sistant mood and psychotic disorders, including major depressive disorder (MDD), bipolar disorder, schizophrenia, and catatonia.² Among these, ECT remains the most effective intervention for severe MDD.¹ The procedure typically involves unilateral (sometimes bilateral) electrode placement over the non-dominant hem-

isphere to deliver an electrical stimulus that induces tonic-clonic seizures. There is a complex interplay between the stimulus parameters, including the position of electrodes, dosage, and waveform of electricity, and its efficacy.

ECT is rarely used as first-line therapy, except in an emergency where the person's life is at risk because of refusal to eat or drink, or in cases of attempted suicide.¹ Most patients fail one or more antidepressant medications before receiving ECT, and those who respond to ECT usually receive continuation pharmacotherapy.³⁻⁵ Regarding its effectiveness, in controlled studies, ECT has a response rate of 70% to 90%. However, in naturalistic population-based community-setting studies, ECT remission rates reach levels less than 50%.³⁻⁵ Despite its effectiveness, ECT is often underutilized due to persistent stigma and limited understanding of modern protocols.⁶

Even though several theories have been proposed for its mechanism of action, it remains poorly elucidated. Potential Mechanisms of action include (a) altered activity of the monoamine neurotransmitter system, (b) effect on neurotrophins, (c) alteration in the concentration of inflammatory factors, (d) epigenetic modifications, (e) structural neuroplasticity, (f) increased neuronal functional changes.⁷ Given the current lack of conclusive data, it is unlikely that any single biomarker will fully define a psychiatric disorder or account for the inherent heterogeneity of psychiatric diagnoses. Instead, it is more plausible that multiple biological mechanisms interact in complex and dynamic ways, collectively contributing to the treatment response.

Optimization of treatment strategies and enabling personalized medicine in the long term are necessities. Currently, there is a lack of clinically useful biomarkers predictive of treatment response.⁸ Therefore, prospective indicators of ECT response are thus in great need. Although treatment resistance in MDD is a robust clinical predictor of poor response for most antidepressant strategies, including ECT, this might be related more to the depressive episode per se than to the intervention.

Regarding 'precision psychiatry', it is envisaged to bring a paradigm shift in clinical psychiatry through the process of integrating data from the complex nature of psychiatric diseases to give biomarkers that can enable more efficacious and personalized treatment strategies.⁹ Precision medicine initiative, as it applies to ECT, can be advanced through the study of epigenetics.¹⁰ Epigenetics comprises a highly increasing area of studies in psychiatry, especially in mood and psychotic disorders, because it acts as a link between environmental factors and the genome, enabling to decipher-

ing of the complex interplay of factors and the nature of psychiatric disorders.¹¹ The novel field of epigenetic effects of ECT is increasingly studied as a key mechanism mediating the impact of environmental factors on brain function and thus enables the research to yield biomarkers.¹²

The individual genetic constitution provides a baseline for the vulnerability to certain diseases, but additional environmental factors are often necessary to provoke the onset. Epigenetics refers to the study of heritable phenotype alterations that do not involve alterations in the DNA sequences, or "the mitotically and meiotically heritable changes in gene expression that do not entail variation in the DNA sequence". Epigenetics is an evolving area of research, especially in psychiatry, due to the nature of psychiatric disorders, where genetic and environmental factors interact. Epigenetics mechanistically links life experiences with the structural DNA code, providing an opportunity to potentially study the effect of both at once.¹³ The three pillars of epigenetic mechanisms are (a) DNA methylation,¹⁴⁻¹⁶ (b) Histone Modifications,¹⁷ (c) RNA interference with non-coding (nc) RNAs.^{7,18} These mechanisms determine the transcriptional state by regulating the access to the DNA sequence of the transcriptional machinery.¹³ Environmental factors seem to influence and play a major role in psychiatric diseases according to the genetic profile of the patients. Epigenetics, being a link between environmental and internal factors, provides the opportunity to further understand this complex interplay of factors and increase the efficacy of treatment methods.¹⁹

The investigation of epigenetic effects induced by electroconvulsive therapy (ECT) offers a unique molecular perspective that integrates previously documented alterations in gene expression, cellular dynamics, neurocircuitry, and functional brain activity. A recent systematic review by Castro et al (2023) synthesized human studies on epigenetic mechanisms related to ECT and identified nine studies, with the majority focusing on DNA methylation and microRNA expression.²⁰ Building on this foundation, the objective of the present systematic review is to comprehensively examine and synthesize the current literature on epigenetic biomarkers associated with ECT response in individuals diagnosed with treatment-resistant major depressive disorder (TR-MDD). Through a critical evaluation of existing studies, this review aims to identify potential molecular signatures that could inform future translational research and advance the development of precision psychiatry approaches in mood disorders. The review critically reassesses prior findings in light of recent methodological advancements, enabling a more

nanced and clinically actionable synthesis of the data. Thus, it not only updates the existing evidence base but also reorients the field toward precision-based interpretations of the epigenetic effects of ECT.

Material and Method

This systematic review was conducted following the PRISMA 2020 guidelines²¹ (figure 1). The aim was to identify, evaluate, and synthesize all relevant studies investigating the relationship between Electroconvulsive Therapy (ECT) response in TR-MDD and epigenetic

mechanisms, including DNA methylation, histone modification, and non-coding RNA expression. A systematic literature search was performed in PubMed and Scopus from 2015 to 2025. The following Boolean queries were used:

- PubMed: (Electroconvulsive Therapy [MeSH Terms] OR Electroconvulsive Therapy [Title/Abstract] OR ECT[Title/Abstract]) AND (Epigenetics [MeSH Terms] OR Epigenetics [Title/Abstract] OR “non-coding RNA”[Title/Abstract] OR “Histone Modification”[Title/Abstract] OR Methylation [Title/Abstract])

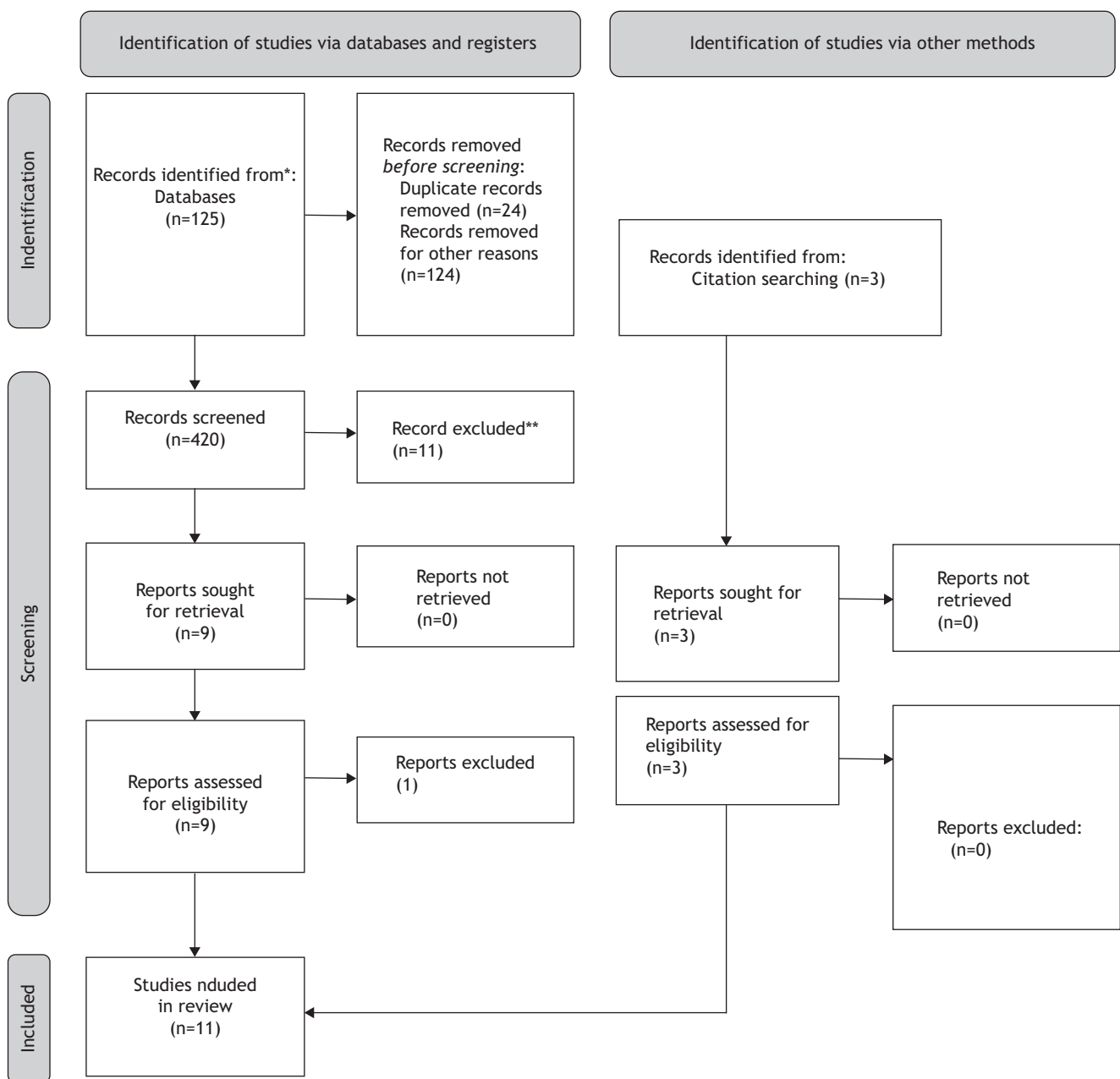


Figure 1. PRISMA flow diagram.

- Scopus: TITLE-ABS-KEY (“Electroconvulsive Therapy” OR ECT) AND TITLE-ABS-KEY (epigenetics OR “non-coding RNA” OR “histone modification” OR methylation)

Additional studies were identified through manual screening of references in eligible articles. Eligible studies were peer-reviewed original research articles that examined the effects of ECT on epigenetic markers in humans diagnosed with MDD and were published in English. Exclusion criteria included animal studies, review articles, conference abstracts, opinion pieces, studies not directly involving ECT, and studies without reported epigenetic outcomes. All references were managed using Rayyan for deduplication and organization. Two reviewers independently screened titles and abstracts, followed by full-text reviews, with disagreements resolved by a third reviewer. Data extraction was conducted using a standardized form and included study characteristics, design, population/sample details, ECT protocol, epigenetic outcomes, and key findings. Due to the heterogeneity of study designs, no formal risk of bias tool was applied. However, potential sources of bias were considered narratively.

Results

This systematic review synthesized current evidence from eleven studies exploring the epigenetic mechanisms associated with electroconvulsive therapy (ECT) in patients with treatment-resistant major depressive disorder (TR MDD) (table 1). The results provide converging but preliminary evidence that ECT may induce epigenetic changes—potentially underlying therapeutic response and symptom improvement. Eight studies investigated the role of DNA methylation as a potential biomarker or mechanistic correlation of Electroconvulsive Therapy (ECT) response, while three studies explored the role of microRNAs (miRNAs) in the context of ECT, utilizing both discovery and validation approaches. In total, ³¹ promising epigenetic biomarkers were examined in the studies (table 2).

ECT and DNA Methylation Findings

Epigenome-Wide and Genome-Wide Analyses

Carvalho Silva et al (2024) conducted a comprehensive epigenome-wide association study (EWAS) to identify methylation changes associated with clinical outcomes of ECT. Longitudinal analyses revealed differentially methylated probes (DMPs) and regions (DMRs) nominally associated with symptom improvement and response status, including genes such as ADARB1, FAM20C, IQCE, and SLC25A24. Female-specific analyses uncovered additional significant and trend-significant DMRs in genes implicated in psychiatric disorders

(ZFP57, GAS7, ADORA2A), trauma exposure (RIPOR2), and immune regulation (TOLLIP, LAT, FAM30A). Although none of the findings survived false discovery rate correction, the results suggest potential biological pathways modulated by ECT, particularly in sex-specific contexts.²²

Similarly, Sirignano et al (2021), using a genome-wide DNA methylation approach, identified two differentially methylated genes, TNKS and FKBP5, surpassing the stringent genome-wide significance threshold, both of which have been previously implicated in stress-response regulation and psychiatric vulnerability.²³

Candidate Gene Methylation Studies

Several studies focused on targeted DNA methylation analysis of stress-related and neuroplasticity-associated genes. Maier et al. (2023) assessed methylation of NR3C1 (glucocorticoid receptor) and POMC, reporting lower baseline NR3C1 methylation in unmedicated depressed controls compared to both ECT-treated patients and healthy controls. ECT induced a reduction in methylation levels of both genes, with responders showing lower post-treatment NR3C1 methylation than non-responders.²⁴

Schurgers et al (2022) observed increased mRNA expression of BDNF, ERK1, and NR3C1 during ECT, with corresponding changes in DNA methylation, highlighting dynamic transcriptional regulation during treatment.²⁵ Similarly, Kleimann et al (2015) found that ECT remitters exhibited significantly lower methylation in BDNF promoter regions (particularly exon I), suggesting epigenetic modulation of neurotrophic signaling as a mechanism of ECT efficacy.²⁶

Moschny et al (2020) performed a genome-wide methylation screen and implicated several novel genes (RNF175, TBC1D14, TRERF1) in ECT response.²⁷ In a separate analysis, while no baseline methylation differences were observed in t-PA and PAI-1 between remitters and non-remitters, cell-type-specific methylation differences were noted, underscoring the relevance of immune cell heterogeneity in peripheral biomarkers.²⁸

In an independent replication study, Neyazi et al (2018) demonstrated higher p11 promoter methylation in ECT responders across two clinical cohorts, reinforcing the potential predictive utility of this locus in antidepressant response.²⁹

ECT and Non-Coding RNA Findings

Genome-Wide and Transcriptomic Analysis

Israel-Elgali et al (2021) conducted a genome-wide assessment of miRNA expression profiles before and

Table 1. Key findings of the included studies.

Author (Year)	N (ECT pts)	Biomarker/ Epigenetic Target	ECT Protocol	Concomitant Medication	Outcome Scale	Key Findings
Kleimann et al 2015	11	BDNF promoter (exons I, IV, VI) methylation; serum BDNF	Thymatron IV; 3 ECT sessions/week over 3, 5 weeks.	medications including antidepressants (n=10), antipsychotics (n=9) remained unchanged	MADRS Score ≤ 12	Lower baseline exon I methylation predicted remission; no serum BDNF change
Gururajan et al 2016	24	miRNA transcriptome (let-7b, let-7c)	bi-weekly brief-pulse bitemporal ECT (not specified further)	Usual antidepressants continued	MADRS $\geq 50\%$ decrease	let-7b/c lower vs controls but neither predicted or changed with ECT
Kolshus et al 2017	16 miRNA cohort; 37 miRNA validation cohort; 97 VEGF-A cohort	miR-126-3p, miR-106a-5p; VEGF-A mRNA	hand-held electrodes on the Spectrum 5000M device; Two group, parallel, double-blind randomised controlled non-inferiority trial comparing high-dose R-unilateral with standard-dose bitemporal ECT; 2 times/week	Mixed; psychotic subgroup often on antipsychotics	HDRS, BPRS-5	Psychotic depression showed elevated miRNAs & VEGF-A; normalised post-ECT. No miRNA changes in non-psychotic depression
Neyazi et al 2018	76 (11 Proof of Concept + 65 replication)	p11 (S100A10) promoter methylation	Not specified	medication remained unchanged	MADRS $\geq 50\%$ decrease	Higher baseline p11 methylation robustly predicted response
Moschny et al 2020a	17	Genome-wide DNA methylation	Thymatron IV; R-unilateral 3 times/weekly up to 4 weeks followed by maintenance ECTs applied only once a week.	medication remained unchanged	MADRS $\geq 50\%$ decrease	8 novel CpGs (RNF175, RNF213, etc.) associated with response
Moschny et al 2020b	first cohort (n=59) second group (n=28)	t-PA (PLAT) & PAI-1 (SERPINE1) DNA methylation (cell-sorted)	Ultra-brief pulse devices [Mecta 5000Q and Thymatron IV]; R-unilateral; 3 times/week up to 4 weeks	medication remained unchanged	HAM-D or MADRS $\geq 50\%$ decrease was interpreted as response, ≤ 7 HAM-D or ≤ 10 MADRS as remission	Strong cell-type methylation differences; no global ECT effect
Sirignano et al 2021	34	Differentially methylated CpG sites, Genome-wide DNA methylation	Thymatron IV; unilateral stimulation with the possibility to change to bilateral stimulation at the discretion of the ECT supervisor; 2-3times/week	Not specified	HDRS-17 Δ or $\geq 50\%$	CpG in TNKS ($q < 0.05$) & FKBP5 were differentially methylated above stringent statistical threshold, related to response

Continues

Table 1. Continued.

Author (Year)	N (ECT pts)	Biomarker/ Epigenetic Target	ECT Protocol	Concomitant Medication	Outcome Scale	Key Findings
Israel-Elgali et al. 2021	17	miRNA & mRNA transcriptome	hand-held electrodes ; unilateral; 2 times/week	Compared with SSRI & ketamine groups	HAM-D24 ≥50 % decrease and a score ≤16 at the end of treatment	↑FKBP5, ↓ITGA2B, ↑miR-24-3p unique to ECT responders
Schurgers et al. 2022	19	mRNA (BDNF, ERK1, NR3C1) & DNA methylation	ThymatronR System IV device; bitemporal electrode position; 2 times/week mean sessions = 6.1 (3-11)	Benzodiazepines were stopped before the first ECT session. Other medications including antidepressants remained unchanged.	MADRS ≥50 % decrease	mRNA ↑ for BDNF, ERK1, NR3C1; correlated with DNA methylation levels.
Maier et al. 2023	31	NR3C1-1F & POMC DNA methylation	Thymatron IV; unilateral; 3times/week up to 10 (±4) sessions	Registry patients on standard medication	MADRS ≥50 % decrease	Responder baseline lower NR3C1 methylation; both genes demethylated acutely
Carvalho Silva et al. 2024	32	EPIC EWAS	Thymatron DG ;Bilateral brief-pulse; 3times/week for 4 weeks	medication remained unchanged	MADRS ≥50 % decrease	Identified multiple DMPs and DMRs related to symptom variation and response, eg. CYB5B, PVRL4, ADARB1, IQCE, SLC25A24. Female-specific DMRs involved psychiatric, trauma-related, and immune-related genes (e.g., ZFP57, POLD4, H19). Pathway analysis highlighted transcriptional, growth, and immune processes.

Table 2. Promising epigenetic biomarkers of ECT response.

Epigenetic Mechanism	Biomarker
DNA Methylation (candidate genes)	NR3C1, POMC, BDNF (exon I, IV, VI), FKBP5, TNKS, SLC25A24, ADARB1, FAM20C, IQCE, RNF175, RNF213, TRERF1, TBC1D14, WSCD1, TOLLIP, LAT, FAM30A, ZFP57, GAS7, ADORA2A, RIPOR2, t-PA, PAI-1, p11 (S100A10, promoter methylation), VEGF-A (mRNA)
microRNAs (miRNAs)	let-7b, let-7c, miR-126-3p, miR-106a-5p, miR-24-3p

after ECT in patients with TR MDD. While no statistically significant changes remained after correction for multiple comparisons, exploratory analyses revealed a potential upregulation of miR-24-3p associated with ECT response, warranting further investigation in larger cohorts.³⁰

Gururajan et al (2016) examined baseline and post-treatment expression of let-7b and let-7c, two miRNAs implicated in neuroinflammation and synaptic plasticity. Although expression levels were reduced

in patients relative to healthy controls at baseline, no significant changes were observed post-ECT, nor was there an association with treatment outcome.⁷

Targeted and Subtype-Specific miRNA Studies

Kolshus et al (2017) employed a discovery-validation framework to examine peripheral blood miRNA and VEGF-A (Vascular endothelial growth factor A) mRNA levels in MDD patients undergoing ECT. In individuals with psychotic depression, levels of miR-126-3p and

miR-106a-5p were elevated at baseline and normalized following ECT, in parallel with reductions in VEGF-A. These changes were not observed in patients with non-psychotic depression, suggesting a potential subtype-specific epigenetic signature responsive to ECT.³¹

Discussion

Across eight studies, DNA methylation emerged as a frequently examined epigenetic marker, with several investigations identifying differentially methylated positions (DMPs) and regions (DMRs) before and after ECT. Notably, Carvalho Silva et al (2024), employing an epigenome-wide association approach, found DMPs and DMRs associated with symptom changes and clinical response, annotated in genes such as ADARB1, IQCE, FAM20C, and immune-related loci such as SLC25A24 and NLRP6. Although these findings did not survive false discovery rate correction, they highlight genes involved in transcriptional regulation, immune signaling, and stress response.²²

Several studies investigated candidate genes previously implicated in HPA axis regulation. Maier et al (2023) and Schurgers et al (2022) both reported altered methylation in NR3C1, the gene encoding the glucocorticoid receptor. Maier et al. found that responders to ECT exhibited lower NR3C1 methylation post-treatment, suggesting normalization of stress-related epigenetic patterns.²⁴ Similarly, Schurgers et al observed increased NR3C1 mRNA and correlated DNA methylation changes during ECT, supporting functional relevance.²⁵

The BDNF gene, a critical gene for neuroplasticity, was also differentially methylated in responders. Kleimann et al (2015) found that ECT remitters had significantly lower BDNF promoter methylation (especially exon I),²⁶ whereas Schurgers et al additionally demonstrated an increase in BDNF mRNA expression, linked to methylation dynamics.²⁵ It has been previously suggested as a biomarker able to distinguish between healthy and depressed subjects.³² These findings support previous hypotheses that BDNF regulation may mediate ECT-induced neuroadaptive processes.

Other genome-wide or targeted studies identified novel epigenetic candidates: TNKS and FKBP5 23; RNF175, WSCD1, TRERF1;27 and p11 (S100A10)²⁹ the latter showing higher promoter methylation among ECT responders in two independent samples. However, some methylation effects were found to be cell-type dependent,²⁸ highlighting the complexity of interpreting peripheral epigenetic data.

The role of non-coding RNAs, particularly microRNAs (miRNAs), was evaluated in three studies. The findings

remain mixed and methodologically heterogeneous. Kolshus et al (2017) conducted a multi-phase investigation, identifying normalization of elevated miR-126-3p and miR-106a-5p levels post-ECT in patients with psychotic depression. These miRNAs are known to regulate VEGF-A, whose mRNA levels also decreased after treatment, indicating a possible coordinated epigenetic and transcriptomic response in specific depression subtypes.³¹ Although the present systematic review focused exclusively on studies involving patients with major depressive disorder (MDD), it is worth noting related work in other psychiatric populations. A recent study by Saglam et al (2024) investigated peripheral microRNA expression in patients with schizophrenia undergoing ECT. The authors examined miRNA expression before and after ECT, identifying differential expression of miR 20a 5p and miR 598 in patients with schizophrenia relative to healthy controls.³² However, no statistically significant changes were observed post-treatment, echoing findings from some MDD studies where miRNA responses to ECT were similarly variable or inconclusive. These results underscore the methodological challenges and inter-individual variability inherent in miRNA biomarker research, and further support the need for larger, diagnosis-specific, and well-powered studies.

In contrast, Israel-Elgali et al (2021) reported no genome-wide significant changes in circulating miRNAs but observed an upregulation of miR-24-3p under less stringent statistical thresholds, suggesting potential sensitivity limitations in miRNA detection methodologies.³⁰ Gururajan et al (2016) similarly found reduced let-7b/c expression in TRD patients relative to controls, but no predictive or treatment-related changes, casting doubt on their utility as dynamic biomarkers of ECT response.⁷

The focus of research in animal studies was to prove a well-established epigenetic effect of the electroconvulsive seizures (ECS), analogous to ECT in animal studies, in the brain of rodents, and provide the knowledge background and a stimulus for further research. The animal studies literature reveals that Electroconvulsive seizures have multiple epigenetic effects that are hypothesized to adjust the therapeutic effects of ECT. Based on the studies included in the de Jong et al review¹² and more recent studies,^{29,34,35} the epigenetic effects of ECS cover all the spectrum of epigenetic mechanisms and include increased histone acetylation in c-Fos, BDNF, and CREB genes; demethylation of BDNF promoter¹², ECS-induced HDAC2 upregulation and decreased H3 acetylation at Arc promoter³² significant decline in H3K9 acetylation in the hippocampus following chronic electroconvulsive seizure,³⁵ p11 promoter and changes in the level of various hippocampal miRNAs.²⁹

Nonetheless, the results cannot be extrapolated to a clinical population of individuals with severe and/or chronic depression, and the results can be considered explorative due to the early phase of neuroepigenetic research and the lack of replication in most of the findings. In contrast to this viewpoint, the most recent animal study of Neyazi et al²⁹ managed to yield results in a proof-of-concept clinical trial. Utilizing a chronic mild stress model of MDD, the group obtained citalopram-resistant rats, and ECS was used. Besides, the group proposed cortical ECS as a more valid procedure to mimic ECT than auricular ECS. The results depict a higher p11 promoter methylation, which was also found in the first clinical trial and was then replicated in a second one. This translational study successfully validates the first biomarker reliably predicting the responsiveness to ECT.

Collectively, the evidence suggests that ECT is associated with measurable epigenetic modifications, primarily in DNA methylation and to a lesser extent in non-coding RNA expression. Genes involved in neuroplasticity (BDNF), HPA axis modulation (NR3C1, FKBP5), inflammation, and synaptic regulation appear to be central mediators. The heterogeneity of findings across studies reflects both the complexity of epigenetic regulation and the diversity of analytic strategies employed. No studies in humans concerning histone modifications were found, leading to the recommendation of future research.

Despite the promising insights presented, several limitations must be acknowledged. The included studies were heterogeneous in terms of sample size, ECT protocols, clinical populations, and methods used to assess epigenetic changes, limiting the comparability of findings. It is important to note that more research is needed before a reliable conclusion can be made, not only in terms of the reproducibility of the results in larger sample sizes. Most studies featured small cohorts and lacked replication, which increases the risk of false-positive results. Additionally, most of the studies did not report or control for key confounders such as medication status, comorbidities, or baseline inflammation, all of which may influence epigenetic signatures. Formal risk of bias assessment was constrained by the variability in study design, but methodological limitations, such as the absence of blinding, small sample sizes, and lack of longitudinal follow-up, were common.

Furthermore, the reliance on peripheral blood as a proxy for brain-based changes introduces an additional layer of uncertainty, given the tissue specificity of epigenetic mechanisms. Due to ethical reasons, the most acceptable sample is peripheral blood, leading the focus of studies to shift in search of biomarkers that

can be traced in the blood. However, since epigenetic changes are cell- and tissue-specific, there is a possibility that some results may not reflect the actual changes in the brain. Though DNA methylation varies between tissues, some inter-individual variations are reflected across the brain and blood in humans.³⁶

From a future perspective, further research is needed to lead to more conclusive results. We recommend research in a multi-omics approach for ECT effects and biomarkers, incorporating longitudinal designs, and considering cell-specific and brain-derived samples where feasible. Strategies that would enhance biomarker validity include adequately powered sample sizes and a priori hypotheses for the role of the markers of interest. Ideally, as stated in the studies choice of prior unmedicated patients will potentially yield more accurate results. Moreover, assessment of SNPs in cases of overlap with areas of interest can eliminate bias and potential influence in the results. Considering research for optimization of therapies for MDD, studies can be conducted for biomarkers for second- and third-line treatment of treatment-resistant MDD, including repetitive transcranial magnetic stimulation (rTMS). There is a plethora of molecular mechanisms involved in the pathophysiology of depression, which can be a target for epigenetic studies. Instances with evidence of epigenetic changes include serotonin transporter-regulating genes, glucocorticoid receptors, and GABA receptors.³⁷

Epigenetics is a promising type of novel biomarker for treatment response for ECT and could improve predictability when used in combination with more established predictors.³⁸ Epigenetic modifications across the genome represent orchestrated phenomena that modulate the transcriptional output of the genetic code. In this sense, identifying the aberrant changes in the epigenetic landscape associated with human disease and the factors promoting such alterations provides the potential for new biomarkers that contribute to clinical decisions. A patient's epigenetic profile may represent a measurable combination of genetic and clinical predictors that could have more prognostic value than either alone, potentially improving physician decision-making and patient experience.^{39,40}

Conclusion

This systematic review synthesized evidence from eleven studies investigating epigenetic mechanisms associated with electroconvulsive therapy (ECT) response in patients with treatment-resistant major depressive disorder (TR-MDD). Across these studies, a total of 31 promising epigenetic biomarkers were identified, including DNA methylation patterns in genes related to

HPA axis regulation, neuroplasticity, inflammation, and immune modulation, as well as miRNAs. While the most consistently investigated mechanism was DNA methylation, a smaller number of studies explored non-coding RNAs, with no human studies addressing histone modifications. The findings suggest that epigenetic changes may play a mediating role in ECT-induced symptom improvement, reflecting underlying molecular adaptations to treatment. However, the overall body of evidence remains preliminary, due to limitations such as small sample sizes, heterogeneity in patient populations and methodologies, lack of replication, and reliance on peripheral blood samples rather than brain-derived tissue. The observed variability in epigenetic signatures across

studies also highlights the complex, cell-type-specific nature of epigenetic regulation, which may limit generalizability. To strengthen the field and move toward clinical translation, future research should focus on well-powered, longitudinal studies with standardized protocols, integration of multi-omics approaches, and consideration of sex-specific and cell-specific effects. Validation of these candidate biomarkers could pave the way for stratified treatment planning and more personalized applications of ECT in psychiatry. Epigenetics holds significant promise as a biomarker platform that could complement existing clinical predictors and enhance our understanding of individual variability in antidepressant response.

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Με κατεύθυνση την Ηλεκτροσπασμοθεραπεία Ακριβείας: Συστηματική ανασκόπηση επιγενετικών δεικτών απόκρισης στη φαρμακοανθεκτική κατάθλιψη

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ΙΣΤΟΡΙΚΟ ΑΡΘΡΟΥ: Παραλήφθηκε 24 Απριλίου 2025/Αναθεωρήθηκε 19 Ιουλίου 2025/Δημοσιεύθηκε Διαδικτυακά 5 Αυγούστου 2025

ΠΕΡΙΛΗΨΗ

Η ηλεκτροσπασμοθεραπεία (ΗΣΘ) αποτελεί μία από τις πιο αποτελεσματικές θεραπείες για ασθενείς με φαρμακοανθεκτική μείζονα καταθλιπτική διαταραχή. Ωστόσο, οι βιολογικοί μηχανισμοί που διέπουν τη θεραπευτική της δράση παραμένουν εν μέρει αδιευκρίνιστοι. Η επιγενετική ρύθμιση έχει αναδειχθεί πρόσφατα ως ένας υποσχόμενος τομέας για την κατανόηση της μοριακής βάσης της απόκρισης στην ΗΣΘ. Σκοπός αυτής της συστηματικής ανασκόπησης ήταν η καταγραφή και σύνθεση των υπάρχουσών μελετών που διερευνούν επιγενετικούς βιοδείκτες σχετιζόμενους με τα θεραπευτικά αποτελέσματα της ΗΣΘ σε ανθρώπινους πληθυσμούς. Διενεργήθηκε συστηματική ανασκόπηση στις βάσεις δεδομένων PubMed και Scopus για μελέτες που δημοσιεύθηκαν μεταξύ Ιανουαρίου 2015 και Μαρτίου 2025, σύμφωνα με τις οδηγίες PRISMA 2020. Κριτήρια ένταξης αποτέλεσαν: (1) πρωτότυπες, αξιολογημένες από ομότιμους εργασίες, (2) διερεύνηση των επιδράσεων της ΗΣΘ σε επιγενετικούς δείκτες και (3) διάγνωση μείζονος καταθλιπτικής διαταραχής. Απόσπασμα δεδομένων αφορούσε στους επιγενετικούς στόχους, τα χαρακτηριστικά των ασθενών, τις παραμέτρους της ΗΣΘ και τα κλινικά αποτελέσματα. Ελήφθησαν υπόψη ο κίνδυνος μεροληψίας και η ετερογένεια των μελετών. Έντεκα μελέτες πληρούσαν τα κριτήρια ένταξης, περιλαμβάνοντας συνολικά 498 ασθενείς με TR-MDD. Στο σύνολο των μελετών εντοπίστηκαν 31 υποσχόμενοι επιγενετικοί βιοδείκτες, που σχετίζονται με τη νευροπλαστικότητα, τη ρύθμιση του άξονα ΥΥΕ (υποθαλάμου-υπόφυσης-επινεφριδίων), τη φλεγμονή, την ανοσιακή σηματοδότηση και τα μη κωδικά RNAs. Οι πιο συχνά μελετημένοι μηχανισμοί ήταν η μεθυλίωση του DNA και η έκφραση miRNA (miRNA). Καμία μελέτη σε ανθρώπους δεν εξέτασε τροποποιήσεις ιστονών. Η παρούσα συστηματική ανασκόπηση παρέχει προκαταρκτικά ευρήματα που υποστηρίζουν τον ρόλο των επιγενετικών μηχανισμών –ιδίως της μεθυλίωσης του DNA και της έκφρασης miRNA– στη ρύθμιση της ανταπόκρισης στην ΗΣΘ σε ασθενείς με TR-MDD. Αν και τα ευρήματα αναδεικνύουν υποψήφιους βιοδείκτες για κλινική ταξινόμηση και ψυχιατρική ακριβείας, οι μικροί πληθυσμοί δειγμάτων και η μεθοδολογική ετερογένεια περιορίζουν τη γενίκευση. Απαιτούνται μεγαλύτερες, τυποποιημένες και προοπτικές μελέτες για την επικύρωση και περαιτέρω αξιοποίηση αυτών των πρώιμων δεδομένων.

ΛΕΞΕΙΣ ΕΥΡΕΤΗΡΙΟΥ: Ηλεκτροσπασμοθεραπεία, φαρμακοανθεκτική κατάθλιψη, επιγενετική, βιοδείκτες, ψυχιατρική ακριβείας.



PSYCHIATRIKI

Published Quarterly by the Hellenic Psychiatric Association

VOLUME 36

JANUARY–DECEMBER 2025

Acknowledgment to Reviewers

The Editorial Board of the Psychiatriki would like to thank everyone who has contributed to the 36th volume, and especially the following expert clinicians and researchers who have served as peer reviewers of the journal:

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We cordially thank you for your invaluable help!

George Konstantakopoulos
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ΨΥΧΙΑΤΡΙΚΗ

Τριμηνιαία έκδοση της Ελληνικής Ψυχιατρικής Εταιρείας

ΤΟΜΟΣ 36

ΙΑΝΟΥΑΡΙΟΣ-ΔΕΚΕΜΒΡΙΟΣ 2025

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Η Συντακτική Επιτροπή της Ψυχιατρικής θα ήθελε να ευχαριστήσει όλους όσους συνέβαλαν στον 36ο τόμο και ειδικά τους παρακάτω ειδικούς κλινικούς και ερευνητές, που εργάστηκαν ως κριτές εργασιών του περιοδικού μας:

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Τριανταφύλλου Καλλιόπη
Τσαμάκης Κωνσταντίνος
Τσατάλη Μαρίαννα
Τσιώνης Αντώνης
Τσόπελας Χρήστος
Τσουβέλας Γιώργος

Φ

Φλωράκης Ανδρέας
Φλώρος Γεώργιος
Φουντουλάκης Κωνσταντίνος
Φρανσίσ Κώστας

X

Χατζημανώλης Αλέξανδρος
Χατζούλης Μιχάλης
Χριστοδούλου Νίκος
Χριστοδούλου Χρήστος

Σας ευχαριστούμε από καρδιάς για την ανεκτίμητη βοήθειά σας!

Γιώργος Κωνσταντακόπουλος
Διευθυντής Σύνταξης