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## Equine-assisted therapy as an adjunctive method in the treatment of recurrent depressive disorder – a case report

Zastosowanie terapii z udziałem koni jako metody wspomagającej w leczeniu zaburzeń depresyjnych nawracających – opis przypadku

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### Abstract

**Background:** The term “animal-assisted therapy” refers to a range of methods in which animals accompany the treatment of patients with various somatic or mental disorders, while “equine-assisted psychotherapy” refers to sessions that involve a psychotherapist and an equine professional working alongside the animal, with the primary goal of improving the mental functioning of the patient. **Materials and methods:** The paper presents a case study of a 48-year-old female patient treated for symptoms of recurrent depressive disorder. A programme of five sessions was developed based on equine-assisted psychotherapy principles. The NEO Five-Factor Inventory, INTE Emotional Intelligence Questionnaire, Beck Depression Inventory II, and UWIST Mood Adjective Checklist were used. **Conclusions:** A series of five sessions based on the equine-assisted psychotherapy principles led to a reduction in the severity of depressive symptoms as measured by the BDI-II scale and a positive change in dominant mood.

**Keywords:** case study, recurrent depressive disorder, animal-assisted therapy, equine-assisted psychotherapy

### Streszczenie

**Wprowadzenie:** Oprócz farmakoterapii i psychoterapii istnieje wiele metod wspierających leczenie zaburzeń psychicznych. Jedną z nich jest terapia oparta na kontakcie ze zwierzętami, w tym terapeutyczne spotkania z udziałem koni. Termin „terapia oparta na kontakcie ze zwierzętami” odnosi się do wielu metod pracy, w których zwierzęta współtowarzyszą w leczeniu pacjentów z różnymi grupami zaburzeń somatycznych czy psychicznych, z kolei „terapeutyczne spotkania z udziałem koni” dotyczy spotkań, w których udział bierze psychoterapeuta i osoba zawodowo zajmująca się końmi. **Cel:** Przybliżenie metody wykorzystującej założenia terapeutycznych spotkań z udziałem koni w pracy z pacjentami cierpiącymi na zaburzenia depresyjne nawracające. **Materiał i metody:** Przedstawiono przypadek pacjentki leczonej z powodu objawów zaburzeń depresyjnych nawracających. Opracowano program spotkań z udziałem koni składający się z pięciu sesji trwających po 1,5 godziny każda. Wykorzystano Inwentarz Osobowości NEO-FFI, Kwestionariusz INTE, Skalę Depresji Becka i Przymiotnikową Skalę Nastroju UMACL. **Wnioski:** Cykl pięciu spotkań opartych na założeniach terapeutycznych spotkań z udziałem koni doprowadził do zmniejszenia nasilenia objawów depresji mierzonych Skalą Depresji Becka oraz do zmiany dominującego nastroju w kierunku zabarwienia pozytywnego (wynik skali UMACL).

**Słowa kluczowe:** zaburzenia depresyjne, opis przypadku, *animal-assisted therapy*, *equine-assisted psychotherapy*

## INTRODUCTION

The positive impact of animal contact on human emotional and physical well-being has been recognised for many years (Aggarwal et al., 2022; Beetz et al., 2012; Charry-Sánchez et al., 2018). Sigmund Freud himself was often accompanied by his dog during therapy sessions. Frequent interactions with animals may be particularly important not only when working with adults, but also when treating children and adolescents (Giraudet et al., 2022). In a study by Hall et al. (2016), which aimed to assess the level of empathy in schoolchildren, the presence of an animal correlated with greater sensitivity and openness to the needs of others. Meanwhile, Huber et al. (2022) highlighted the positive effect of animal-assisted interventions in significantly reducing the level of experienced stress and feelings of anxiety among students.

The term “animal-assisted therapy” (AAT) refers to a range of therapeutic approaches in which animals are used in the treatment of patients suffering from a variety of somatic or psychiatric disorders (Pichot and Coulter, 2011). Using a 12-week proprietary treatment programme, Shih and Yang (2023) confirmed the positive effect of AAT on the level of social skills and subjectively rated quality of life of individuals treated for schizophrenia (the study was conducted during the COVID-19 pandemic). In a randomised controlled clinical trial of AAT in patients diagnosed with schizophrenia, Chen et al. (2021) observed an improvement in symptom severity, as measured by the Positive and Negative Syndrome Scale, and a reduction in perceived stress using the Depression Anxiety Stress Scales Assessment. Fennig et al. (2022) evaluated the efficacy of AAT in the treatment of patients with eating disorders (meta-analysis of ten randomised trials, eight studies with horses, one with dogs, one with dolphins; subjects over 11 years of age). The reported benefits of AAT include increased cognitive flexibility, reduced need for control and greater self-confidence, as well as a reduction in the severity of eating disorder symptoms. In contrast, Guillen Guzmán et al. (2022) demonstrated the benefits of long-term daily contact with animals in a psychiatric day care unit for children. In particular, the authors reported a significant increase in emotion regulation skills in the study group (23 children under the age of 13). Rehn et al. (2023) emphasised the benefits of AAT for children and adolescents on the autism spectrum (positive changes were observed in the cognitive, social, emotional, and behavioural domains of the participants). Similarly, Prothmann et al. (2009) observed that children on the autism spectrum readily interacted with dogs, and that the duration of interaction with the animal was significantly longer than with another human.

Based on the findings of Kamioka et al. (2014), AAT can be considered an effective treatment for mental and behavioural disorders such as depression, schizophrenia, and alcohol/drug addiction, as it is grounded in a holistic approach involving animal interaction. In contrast, Lai

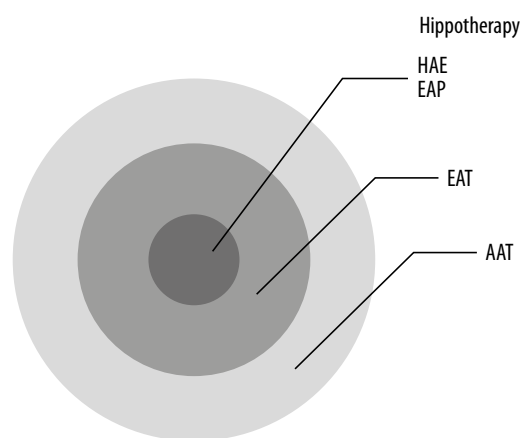
et al. (2019) attempted to evaluate the efficacy of AAT in the treatment of people with dementia. However, their systematic review of the literature was inconclusive. One of the reasons cited by Lai et al. (2019) was the small number of randomised clinical trials conducted on this topic, considerable heterogeneity among studies and, above all, marked differences in outcome measures and interventions. Interestingly, some studies suggest benefits of using so-called pet robots in therapeutic work with this group of patients (Koh et al., 2023).

An offshoot of AAT is a therapeutic method that utilises a series of human-horse interactions. Several terms have been used in the literature to describe this approach, including hippotherapy, horse-assisted education (HAE), equine-assisted therapy (EAT), and equine-assisted psychotherapy (EAP) (Hallberg, 2017). It should be noted, however, that these terms are not interchangeable (Fig. 1).

Hippotherapy is primarily based on human-horse contact and riding. It aims to restore and improve the individual's physical health and fitness (Strumińska, 2003). Incorporating hippotherapy into the treatment process can complement pharmacotherapy on many levels and assist in the elimination of social and emotional deficits (Czelej et al., 2022).

HAE is a method aimed at improving interpersonal and intrapsychic skills through contact with animals. Its goal is to increase the effectiveness of the patient's own functioning in both professional and private life (Wiatrowska and Popławska, 2013). According to Wiatrowska and Popławska (2013), pioneers of the HAE method in Poland, an adult can develop communication and leadership competencies, as well as social skills, in the company of horses.

EAP refers to sessions involving a psychotherapist and an equine professional, in addition to the animal, with the primary goal of improving the mental functioning of the



**AAT** – animal-assisted therapy; **EAP** – equine-assisted psychotherapy; **EAT** – equine-assisted therapy; **HAE** – horse-assisted education.

*Fig. 1. Types of interaction with horses that have therapeutic potential*

patient/client. EAP is believed to have therapeutic potential because horses actively seek human contact. These animals naturally become therapists, and clients/patients actively engage in interactions with them (Lee and Make-  
la, 2015). Numerous studies indicate the effectiveness of EAP in the treatment of depressive and anxiety disorders (Zoccante et al., 2021).

EAT is the broadest of the above terms. It is a type of experiential therapy that includes all activities involving horses to promote human physical and mental health (Masini, 2010). It may be used with patients being treated for substance abuse and addiction; behavioural, mood, and eating disorders; attention deficit hyperactivity disorder; autism spectrum disorders; or post-traumatic stress disorder (PTSD) (Sudhadevi and Surya, 2020). EAT has been used with children and adolescents, as well as adults and the elderly (Ratcliffe and Sanekane, 2009). Anderson and Meints (2016) found that EAT reduced atypical social behaviours, increased feelings of empathy, and improved social skills in adolescents over the age of 15. Gabriels et al. (2015) found improvements in social behaviour and communication skills in children and adolescents aged 6 to 16 years after regular encounters with horses. An interesting study on the effectiveness of EAT in the treatment of PTSD was conducted by Earles et al. (2015). Their project involved 16 volunteers who presented symptoms of PTSD (score >31 on the PTSD Checklist) following a traumatic event. Participants took part in six two-hour equine sessions, held once a week. After the intervention, they reported significant reductions in posttraumatic stress symptoms ( $d = 1.21$ ), reduced emotional reactivity ( $d = 0.60$ ), reduced levels of experienced anxiety ( $d = 1.01$ ), and significant reductions in depressive symptoms ( $d = 0.54$ ). In addition, participants showed a significant increase in the use of mindfulness strategies ( $d = 1.28$ ), and reported a decrease in the frequency of alcohol use ( $d = 0.54$ ). EAT has also been shown to promote lower blood pressure in elderly populations (Mello et al., 2021).

The aim of this article is to present a therapeutic method using the principles of EAP in working with patients with recurrent depressive disorder (RDD).

## SURVEY METHODOLOGY

Candidates for the study were recruited via an online form posted on social media, which included a description of the study and the eligibility criteria. One person was randomly selected from the pool of individuals who volunteered to participate in the study.

### Inclusion and exclusion criteria for participation in the study

Inclusion criteria: age 25–55 years; diagnosis of RDD (F33); not engaged in regular psychotherapy of any kind during the study period; pharmacotherapy with a fixed dose of

antidepressants for a maximum of two months (counted up to the start of the study); Beck Depression Inventory score >11; no suicidal ideation and/or tendencies prior to study entry and during the study; and provision of informed consent to participate in the study.

Exclusion criteria: age <25 and >55 years; central nervous system damage; comorbid Axis I or II diagnoses (according to ICD-10 criteria); intellectual disability; exacerbation of somatic illness; engagement in regular psychotherapy of any modality during the study; dose change/discontinuation of antidepressant medication within two months prior to study entry; Beck Depression Inventory score <11; presence of suicidal ideation and/or tendencies prior to study entry; lack of informed consent to participate in the study; and severe fear of contact with horses.

The inclusion criteria for the study were based on the diagnostic criteria for RDD (F33) included in the ICD-10 Classification of Mental and Behavioural Disorders (World Health Organization, 1992), and assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996).

A psychiatrist and a clinical psychologist conducted the eligibility screening for the study.

The mental state of the participant was continuously monitored by the above-mentioned specialists to assess the risk of suicide.

## Ethics

The procedure and conduct of the study were approved by the Bioethics Committee of the Medical University of Lodz (Resolution No. RNN/41/22/KE of 08/02/2022). The participant was informed that she could withdraw from the study at any time. The patient's personal data was coded to protect her privacy, and all information collected was used exclusively for scientific purposes.

## Research tools and survey procedure

The following tools were used in the study:

- Socio-demographic survey to collect basic demographic data.
- NEO-FFI Personality Inventory by Costa and McCrae (1992) – a questionnaire for assessing personality traits included in the popular five-factor (Big Five) model. The results allow for a complete description of the subject's personality.
- INTE Emotional Intelligence Questionnaire adapted by Ciechanowicz et al. (2000) – used to measure emotional intelligence, understood as the ability to recognise, understand, and control emotions in oneself and others, as well as the ability to use emotions effectively in guiding behaviour.
- Beck Depression Inventory – Second Edition (BDI-II) (Beck, 1996) – used to assess the severity of depressive symptoms.

- UWIST Mood Adjective Checklist (UMACL) (Matthews et al., 1990) – a test designed to measure mood, defined as an affective experience of moderate duration (at least a few minutes), unrelated to a specific object or related to a quasi-object, and involving three dimensions of core affect, i.e. energetic arousal, tense arousal, and hedonic tone.

The socio-demographic questionnaire, the NEO-FFI questionnaire, and the INTE scale were administered once before the respondent entered the project. The BDI-II and UMACL were administered before the start of the procedure and at each of the five subsequent sessions. The subject's thoughts, feelings, and behaviours were also recorded during each session (the programme was based on the principles of cognitive-behavioural psychotherapy).

This article is part of a project evaluating the possible relationship between the type and frequency of therapeutic contact with horses and changes in the expression at the mRNA level of the gene encoding the oxytocin receptor (OXTR) in individuals suffering from depression. The questionnaires used in the study allow for the assessment of respondents' personality traits, which may act as mediators between the variables studied, as well as for the monitoring of respondents' emotional state across various dimensions. For the purposes of the study, a programme of equine-assisted sessions was developed based on EAP principles. It comprised five sessions of 1.5 hours each. The activities were facilitated by a psychologist who was a certified HAE facilitator, a certified member of the Equine Assisted Growth and Learning Association (Eagala), and a licensed riding instructor. The psychologist had received training in working with horses and had experience in providing psychological support. Each session involved two horses trained and prepared for this type of work. The sessions

took place at a stable equipped for such activities. The patient independently drove to the session site. All sessions were conducted outdoors, in a fenced area, without interference from third parties.

The session procedure is presented in Appendix 1. A session report was developed based on training materials on HAE (Wiatrowska, 2015) and EAP (Eagala, 2019).

## CASE DESCRIPTION

Patient AS, age 48. She has been receiving intermittent treatment for RDD for five years. She was diagnosed with a third episode prior to her participation in the study. She had no psychiatric hospitalisation or psychotherapy prior to the study.

The patient lives in a village near Łódź, Poland. She is married and has one adult child (daughter, 25 years old). She evaluates her family relationships as satisfactory.

She holds a university degree and has worked in a managerial position at an oil company for almost 20 years. The patient is currently on sick leave due to a deterioration of her mental health. At the time of her participation, the patient had been taking a serotonin-norepinephrine reuptake inhibitor (Faxolet) at a dose of 300 mg/day for four weeks.

She was born and raised in a complete family and has one older brother. There is no reported family history of psychiatric disorders.

The patient complains of subjectively perceived decreased efficiency of cognitive processes (mainly attention and memory), feelings of fatigue, anhedonia, sleep disturbances (difficulty falling asleep, waking up in the morning hours, non-restorative sleep), appetite suppression, weight loss, avoidance of social contacts, intrusive negative thoughts, and resignation thoughts. She emphasised problems with

Study participant:

Meeting number	Date	Duration	Procedure	Respondent's emotions, thoughts and behaviours
1		90 min	Explanation of safety rules and the basic signals communicated by horses. Observation of a herd of horses staying in a meadow	
2		90 min	Staying in the meadow with two horses (Mimi and Krakowiak). Observation, conscious breathing, touch	
3		90 min	Individual work with a horse (Mimi) – grooming, touching, cleaning, and feeding the animal	
4		90 min	Individual work with a horse (Krakowiak) in a round pen with a diameter of 18 meters – leading the animal on a rope, moving freely	
5		90 min	Staying in the meadow with both horses. Observation, conscious breathing, summary of all sessions	

Temperament and character of horses selected for the study based on the Profile of Horse Temperament and Character – PETC FA1 (Suwała et al., 2016):

Mimi – a high desire to be in the presence of humans, medium energy levels, low skittishness, high sensitivity, strong adaptability, high subordination, low aggressiveness, a high degree of independence.

Krakowiak – a low desire to be in the presence of humans, low energy levels, low skittishness, low sensitivity, medium adaptability, medium subordination, low aggressiveness, a high degree of independence.

Appendix 1. Report from therapy with horses

motivation and a lack of involvement in daily life. She denied the presence of suicidal ideation or tendencies.

### Test results

The results of the psychological tests performed are shown in the Tabs. 1 and 2.

The results of the NEO-FFI questionnaire indicate that the subject's emotional responses are appropriate to both the stimuli and situation. The patient has no difficulties in social interactions. She is eager to take on new challenges and tends to avoid conflict situations (tries to find solutions that lead to alleviating the situation).

The results of the INTE questionnaire testify to the respondent's high level of emotional intelligence, both in terms of understanding her own emotions and in her ability to adequately recognise emotions in others. This indicates that she is able to identify her emotions and regulate them appropriately according to her own needs and the demands of the environment, which correlates with her low neuroticism score on the NEO-FFI.

On the day of the study, the patient's BDI-II questionnaire score indicated a moderate severity of disease symptoms (21 points, range 22–26 points). The score on the same questionnaire after a series of equine-assisted sessions was 17 points (mild severity of disease symptoms, range 12–19 points). The change was found in statements related to anxiety (decreased perceived anxiety), energy (increased perceived energy), sleep (improved sleep quality), and irritability (decreased irritability).

The results of the UMACL questionnaire taken before the first session indicated a predominance of negative emotions. In contrast, the results of the same test taken after a cycle of five therapy sessions implied a positive change in the dominant mood (an increase in hedonic tone, a decrease in the level of tense arousal).

NEO-FFI	
Name of the scale	Sten
Neuroticism	4
Extraversion	5
Openness to experience	6
Agreeableness	7
Conscientiousness	3
INTE	
Name of the scale	Sten
Ability to use emotions in supporting thinking and action	10
Ability to recognise emotions	8
Overall result	9
INTE – Emotional Intelligence Questionnaire; NEO-FFI – NEO-FFI Personality Inventory. Sten scale: 1–2 – very low scores; 3–4 – low scores; 5–6 – average scores; 7–8 – high scores; 9–10 – very high scores.	

Tab. 1. Results of the NEO-FFI and INTE questionnaires taken once at the beginning of the sessions

Interviews conducted with the patient showed that the respondent felt considerable tension at the start of each meeting. She complained of intrusive thoughts, attention problems, headaches, and a general drop in mood. After the sessions, she felt more positive emotions (calmness, joy). She repeatedly said, "I feel relaxed, and the intrusive, pessimistic thoughts are gone". She stressed that during the meetings she was much more attentive to the experience and focused on the present moment. She was eager to attend each of her visits. During the summary of the entire series, she referred not only to the sessions themselves, but also to a noticeable change in her daily functioning. She observed that her motivation to become active and willingness to interact with others had increased. In the final interview, she said: "Today is another day of therapy with horses. These are the moments when I feel the here and now. The mind gets caught up in observation and stillness. Nothing else exists, nothing else matters. All the clutter in my head dissolves in the experience of this one and only moment. The chase of thoughts subsides. My body relaxes, the tension disappears, and I feel the muscles loosen. This is where life stops. Time slows down, as if it were the only place in the world. I'd like to stay here. To enjoy the simple life, surrounded by animals and nature. The noise, flashing lights, fast-moving cars, pictures, advertisements, letters, words – words that have no meaning here... all that is gone. Nothing interests me at the moment. Krakowiak and me. He tastes the grass with such an appetite. I'm watching him. He is always living in this one moment. I learn from him. He walks with me, although he is so big and strong. I feel grateful that I live, I experience, I am".

### DISCUSSION

The case study presented allows for the consideration of EAT as an alternative or adjunct to evidence-based

BDI-II		
On the day of study inclusion	21 (moderate severity of depressive symptoms)	
On the day of the last meeting	17 (mild severity of depressive symptoms)	
UMACL	Name of the scale	Sten
On the day of study inclusion	Hedonic tone	4
	Tense arousal	7
	Energetic arousal	5
On the day of the last meeting	Hedonic tone	6
	Tense arousal	5
	Energetic arousal	5
BDI-II – Beck Depression Questionnaire; UMACL – UWIST Mood Adjective Checklist. Sten scale: 1–2 – very low scores; 3–4 – low scores; 5–6 – average scores; 7–8 – high scores; 9–10 – very high scores.		

Tab. 2. Results of BDI-II and UMACL questionnaires taken at the beginning and end of the sessions



therapies. These encounters directly affect the core components of anxiety and symptoms of depression (Wilson et al., 2017). Contact with a horse induces positive emotions, helps reduce stress, increases alertness, and improves attention. Why does this happen? The literature suggests that humans treat the animal as a positive internal object that soothes and comforts. Nonverbal contact with the animal can be compared to a child's primary relationship with a caregiver, influencing later emotional and social development (Stern et al., 2005). In addition, horses, like human psychotherapists, play an important role in modifying attachment styles and enabling further exploration of the patient's dominant relational patterns (Bachi and Parish-Plass, 2017).

In the case presented here, a shift in the dominant mood toward a positive tone was achieved, as well as a marked decrease in the patient's perceived tension (evaluation based on the tools used). The patient's subjectively reported level of functioning also improved significantly, as reflected in the statements quoted above. The results are consistent with literature reports describing the effectiveness of EAT in the treatment of depressive symptoms (Artz et al., 2021, Kinney et al., 2019, O'Haire et al., 2015).

Therapy with animals tends to be remembered by patients for a long time. One study compared the experiences of female patients participating in traditional psychotherapy and parallel alternating sessions of psychotherapy with horses. Data collected 15 years after the end of the sessions showed that the experiences directly related to the contact with the animals were best remembered (Tuuvast et al., 2017).

In a study involving adolescents, EAP therapists found increased self-confidence, elevated self-esteem and assertiveness, improved emotional regulation and self-control, greater resourcefulness, and decreased undesirable behaviours. Therapists attributed these improvements to the experiential component of the therapy and the inclusion of the horse as a therapeutic medium (Berget and Braastad, 2011). The experiential nature of the encounters gave the adolescents the opportunity to try out and "practise" new behaviours, according to social learning theory. The presence of the horse as a therapeutic medium also provided the therapist with the opportunity for "pure" observation of the adolescents' behaviour and emotions (horses do not engage in complex interpretations as human therapists do) (Lentini and Knox, 2009).

A study entitled L.A.S.S.O. (Leading Adolescents to Successful School Outcomes) examined the impact of equine-assisted learning (EAL) on levels of hope and the severity of depressive symptoms in adolescents at risk for depression. A longitudinal repeated measures experimental design was used. Participants were randomly assigned to a treatment group (Group I) and a control group (Group II). Those in the treatment group received five weeks of EAL training in addition to standard pharmacological and psychotherapeutic treatment, while those in the control group received no intervention. The results indicated a significant reduction

in depressive symptoms in the treatment group (Frederick et al., 2015).

Research on human-horse relationships also suggests that these animals are highly sensitive to human emotional states. Gherke et al. (2011) observed that a horse's heart rate variability (HRV) changes in response to the emotions of people in its immediate environment. When the human was affected by strong negative emotions or depressive states, the horse mirrored this state, as reflected by its ECG readings and immediate behavioural response. In addition, the study by Pohl et al. (2018) showed that six months of participation in a workshop with horses increased self-awareness ratings and the ability to manage emotional resources, and improved social sensitivity and readiness to deepen relationships with others.

Interviews with therapists using equine-assisted methods to work with adolescents experiencing depressive symptoms revealed the great potential of this approach. Therapists claimed that it produced results much more quickly than traditional sessions, and improvements in patient functioning were seen at each session. Adolescents showed enhanced self-control, better emotion regulation, and a decrease in the frequency of undesirable behaviours. In addition, teacher reports indicated that they observed students' renewed engagement in school life and a significant increase in the frequency of peer interactions (Trotter and Baggerly, 2019).

The number of scientific studies documenting EAT has increased in recent years. However, there remains a lack of standardised and validated tools to assess the effectiveness of the described therapeutic modalities. Some hope comes from the use of a digital EAT assessment tool based on the International Classification of Functioning, Disability and Health (ICF). This 80-item pilot tool is considered a first step toward a standardised assessment of EAT outcomes. Establishing a common language for measuring therapeutic effects could increase the synchronisation and integration of EAT interventions within international health care systems (Stolz et al., 2022).

## PERSPECTIVE AND FURTHER RESEARCH DIRECTIONS

The presented study is part of a scientific project entitled "The effect of sessions conducted with the Horse Assisted Education method on oxytocin levels in individuals with recurrent depressive disorders", which aims to test whether there is an association between the nature and frequency of therapeutic contact with horses using HAE and improvements in mental status, along with increased expression at the mRNA level of the gene encoding OXTR in patients suffering from RDD.

The case study shows an improvement in the participant's psychological indicators of the subject (reduced intensity of depressive symptoms and enhanced mood).

The findings align with data identified in the literature review.

The next step should be to expand the study protocol and include a larger number of patients to evaluate its efficacy.

## LIMITATIONS OF THE STUDY

Lack of validated tools to assess the effectiveness of therapy and a standardised and tested session protocol.

## CONCLUSIONS

A series of five sessions based on the EAP principles led to a reduction in the severity of depressive symptoms as measured by the BDI-II and a positive shift in dominant mood (UMACL scale score).

### Conflict of interest

*The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.*

### Author contribution

*Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data: KR, MET. Writing of manuscript: KR, KZ, MET. Critical review of manuscript: KZ, MET. Final approval of manuscript: MET.*

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