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&
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LIFESTYLE MEDICINE

**LIFESTYLE MEDICINE AS A MEAN OF AMELIORATING WITHDRAWAL
ANTIDEPRESSANTS' EFFECT: A SCOPING REVIEW AND A CASE STUDY**

by

Elizaveta Kuznetsova

Supervisory Team: Prof. Christina Karatzaferi, University of Thessaly, GR
Prof. Giorgos K. Sakkas, University of Thessaly, GR
Prof. Ioannis Stefanidis, University of Thessaly, GR
Scientific Advisor: Dr. Petros C. Dinas University of Thessaly, GR

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Author's Contribution Statement

I certify that I am the author of this thesis and that any assistance I have had in its preparation is fully acknowledged and referenced in the following text. I have also cited any sources from which I have used data, ideas or words, whether they are quoted exactly or paraphrased. I also certify that this thesis was prepared by me personally specifically for the requirements of obtaining a Master's degree in Lifestyle Medicine by the University of Thessaly. I declare that I will respect co-authorship rights in any linked scientific publication and/or presentation stemming from this thesis, in accordance to my signed affirmation, and in respect of the principles of ethics in research. Likewise, I declare I will recognize any funding sources and will acknowledge my affiliation to the University of Thessaly during the preparation of this work in any future presentation.

Elizaveta Kuznetsova

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Abstract

Introduction: Lifestyle medicine is a branch of evidence-based medicine that uses holistic approach for better health, well-being and disease prevention.

During last decades antidepressants consumption constantly raises. There are some risks regarding to that: firstly, antidepressants over-indication, secondly, cancelling therapy without proper control. Also, there are several withdrawal effects, related to antidepressants discontinuation, including dizziness, fatigue, headaches, insomnia and others, including reoccurrence initial problem [1] [2]. According to some data, it might not be safe to consume some antidepressants during pregnancy [3] [4] [5]

Therefore, the idea to support patients during antidepressants discontinuation is relevant and requires further investigations.

Aims: The aim of this study is to check possible approaches in supporting patients with discontinuation of antidepressants therapy, and to provide working scheme of this support, using lifestyle medicine intervention.

Methodology: Scoping review was conducted for checking current state of the art [6] Additionally, 1,5-year support program for antidepressants discontinuation accomplished by lifestyle medicine counselling was performed and presented as a case study.

Results: During our 1,5-year protocol, we worked with following lifestyle medicine pillars: physical activity, nutrition, stress management, sleep hygiene, social connection and environmental exposure. Such pillar as substance use were not discussed due to absence of this problem for the patient. Additionally, sexual health was not discussed according to patient wish. In our case study, antidepressants were successfully discontinued without serious adverse effects.

Discussion: There is no data in the literature about the existence of such a program previously. The most used support method for antidepressants discontinuation is CBT. However, different lifestyle methods are used for variety of health issues Considering the potential of this program to be included in future recommendations after a sufficient period of observation

Keywords:

Lifestyle medicine, withdrawal symptoms, antidepressants discontinuation, lifestyle pillars, cognitive behavior therapy.

Резюме

Введение: Лайфстайл медицина — это ветвь доказательной медицины, которая использует целостный подход по улучшению качества жизни и профилактики различных заболеваний за счет изменения привычек и здорового образа жизни. В последнее годы общество и ученые обратили внимание на рост количества людей, которые используют антидепрессанты. С одной стороны есть риски избыточного назначения подобной терапии, а с другой - бесконтрольной отмены препаратов. Известно, что отмена антидепрессантов часто сопровождается неблагоприятными симптомами, в том числе тошнотой, усталостью, головной болью, бессонницей и другими, а также может привести к риску рецидива заболевания, в связи с которым данная терапия была назначена [1] [2]. Также, по ряду данных, применение антидепрессантов при беременности может оказать влияние на здоровье плода [3] [4] [5]. Поэтому вопрос аккуратного прекращения терапии антидепрессантами, используя целостный подход лайфстайл медицины, может оказаться оптимальным решением данной проблемы и требует дальнейшего изучения.

Цель: Изучение существующих в настоящее время подходов помощи пациентам, которые прекращают прием антидепрессантов, а также разработка методики поддержки таких пациентов с использованием лайфстайл медицины.

Методология: Для оценки текущей ситуации поддержки пациентов, прекращающих прием антидепрессантов, был выполнен обзор существующих исследований [6]. В представленном клиническом случае была применена на практике 1,5-летняя программа поддержки отмены антидепрессантов с использованием лайфстайл медицины.

Результаты: За время 1,5-летнего протокола в описанном нами клиническом случае, были проработаны основные главы лайфстайла, такие как питание, физическая активность, работа со стрессом, гигиена сна, а также социальные взаимодействия и воздействие на окружающую среду. Работа с вредными привычками не проводилась по причине их отсутствия, сексуальное здоровье не обсуждалось, учитывая пожелания пациентки. В описанном нами клиническом случае, антидепрессанты были успешно отменены, без значительных побочных эффектов.

Обсуждение: В литературе не было получено данных о существовании подобной программы ранее. Наиболее используемым методом поддержки при отмене антидепрессантов, является КПТ. Тем не менее, отдельные методы и главы лайфстайл медицины используются при различных заболеваниях. Учитывая полученные нами результаты, возможно дальнейшее рассмотрение потенциала этой программы для включения в будущие рекомендации после достаточного периода наблюдения и исследования на большей выборке.

Ключевые слова:

Лайфстайл медицина, синдром отмены, отмена терапии антидепрессантами, основы здорового образа жизни, когнитивно- поведенческая терапия.

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List of abbreviations

AD – Antidepressants
ADM – Antidepressant medication
AIDS – The Anxiety Disorders Interview Schedule for DSM-IV
AN – Anxiety disorder
ASI – Anxiety sensitivity index
BAI – Beck Anxiety Inventory
BDI – Beck Depression Inventory
CBT – Cognitive behavioral therapy
CBT-PR – Cognitive behavioral therapy for the prevention of recurrence
CGI – Clinical Global Impression Scale
CID – Paykel Clinical Interview for Depression
CM – Clinical management
DALYS – disability-adjusted life-years
DAS – Dysfunctional Attitude Scale
DSM – Diagnostic and Statistical Manual of Mental Disorders
EFTs – Emotional Freedom Techniques
EK – Elizaveta Kuznetsova
EQ-5D-3L – Health-related quality of life using the three level version
FQ – Fear questionnaire
GAD – Generalized anxiety disorder
HDRS – Hamilton Depression Rating Scale
HPQ – WHO's Health and Work Performance Questionnaire
IDS-C – Inventory for Depressive Symptomatology-Clinician
IDS-SR – Inventory of Depressive Symptomatology–Self Report
KIMS – Kentucky Inventory of Mindfulness Skills
LEIDS – Leiden Index of Depression Sensitivity
LM – lifestyle medicine
mADM – maintenance antidepressant medication
MADRS – Montgomery-Åsberg Depression Rating Scale
MAOIs – monoamine oxidase inhibitors
MBCT – Mindfulness-based cognitive therapy
MBCT-TS – MBCT with support to taper or discontinue antidepressant treatment

MBSR – Mindfulness-Based Stress Reduction
MDD – Major depressive disorder
MI – Mobility inventory
MINI – Mini-International Neuropsychiatric Interview
MSCL – medical comorbidities using the Medical Symptom Checklist
PCT – Preventive cognitive therapy
PD – Panic disorder with or without agoraphobia
PDSS – Panic Disorder Severity Scale
PLA+Clin – Placebo + clinical management
PTSD – Post-traumatic stress disorder
QLESQ – Quality of Life Satisfaction Questionnaire
RCT – randomized control studies
RRS – Ruminative Responses subscale of the Response Styles Questionnaire
SCID – Structured Clinical Interview for DSM-IV
SCS – Self-Compassion Scale
SDS – Sheehan Disability Scale
SIGH-D – Structured Interview Guide for the Hamilton Depression Rating Scale
SPRAS – Sheehan Patient-Rated Anxiety Scale
SR – systematic review
SSRI – selective serotonin reuptake inhibitor
SNRIs – serotonin/norepinephrine reuptake inhibitors
TCAs – tricyclic antidepressants
WHOQOL-BREF – The World Health Organization Quality of Life assessment

1. Introduction

According to the definition, that is adopted by the ELMO Scientific Council, Lifestyle Medicine is a branch of medicine which has as a goal to maintain optimal health and to prevent, treat and reverse chronic illness across all life stages. The health interventions used in lifestyle medicine include evidence based behavioral strategies, while considering equity and sustainability, to enhance self-management skills for optimizing nutrition, sleep hygiene, stress management, social connection, sexual health and fertility, physical activity and minimizing substance use and environmental exposures [7]. Some lifestyle recommendations are already used in guidelines for cardiovascular disease and studies for cancer patients, especially such pillars as physical activity and nutrition [8] [9] [10]

There are multiply studies, that such interventions as physical activity, nutrition, stress management and sleep hygiene have positive relation to improve mental health [11]

It is important to mention, that considerable section of the population suffers from mental illness, yet due to regional variations in diagnostic standards and perceptions of mental health, addressing and comprehending the prevalence of mental illness can be challenging. The most common conditions for antidepressants (AD) are anxiety and depression.

In 2022, the UK, Portugal, and Iceland were the top three nations in the Organization for Economic Cooperation and Development for antidepressant usage. Antidepressant use at the time was roughly 157 specified daily doses per 1,000 persons in Iceland. Additionally, high percents of antidepressants usage are in America and South-East Asia. [12].

Last trends show global increase in antidepressant consumption and long-term usage of these medications. At least in 30-50% of cases of long-term therapy we meet lack of evidence-based reason of admission the therapy. Overuse of antidepressants might be underestimated. Nonetheless, there is a dearth of high-confidence data concerning the efficacy and security of methods for stopping long-term antidepressants.

As it was mentioned in Cochrane Database Systematic Review, published in 2021, that it is not clear, how to process safely discontinuation of antidepressants without withdrawing effects and relapse, that requires re-admission of therapy. Also, in many cases it is insufficient what were initial indications for the antidepressant therapy. Other obstacle was absence of unified program for the withdrawal of antidepressants and control of withdrawal syndrome in patients. For future investigations, authors suggest to control patients who stop antidepressants more carefully, use CBT and MBCT to support

antidepressants discontinuation. Also, less resource-intensive and more accessible psychological approaches can reach more people and should be investigated. Moreover, authors suggested to evaluate effectiveness Discontinuation-Emergent Signs and Symptoms Scale (DESS) for monitoring therapy discontinuation [2].

Therefore, the antidepressants discontinuation requires further investigation, especially due to absence well-designed program for patients support during this process.

Literature Review

1. Mental health issues globally

Depressive and anxiety disorders accounted for more than 970 million prevalent cases globally in 2019 [13]. According to WHO, it is 1 in every 8 people and this number has even increased by 28% due to COVID-19 pandemic [14]. COVID-19 pandemic, political conflicts and instability, human rights issues, and environmental events all these events have their impact on the incidence of mental health diseases [15]. Due to COVID-19, over 53.2 million cases of depression and 76.2 million anxiety cases additionally appeared. Risks groups were lined out, including burn out and other mental issues of healthcare workers [16] [17] [18].

Depressive and anxiety disorders are the most frequent conditions among population [15]. Moreover, there is a high percent of adolescence with mental disorders. It is about 13% globally with prevalence of anxiety and depression up to 40% among all mental health issues [19].

Nonetheless, the most serious aspects of mental health are disability and the risk of suicide, which makes a serious contribution to overall mortality [20] [21]. This systematic review provides an updated analysis of global data on gaps in treatment coverage for major depressive disorder. Unfortunately, we do not have common relevant data due to the lack of large amounts of data from low- and middle-income countries, that can contribute to global epidemiology [15]. One should not underestimate the current trends associated with the increase in mental problems around the world. However, it is important to discuss and evaluate the most effective and safest methods of care.

Factors, that may influence mental disorders, include gender, age, health conditions, education level, income and social status and also environmental factors [15].

In EU one of the most frequent case of mortality in advanced age are mental and behavioral disorders and it is 22 times bigger comparing to overall mortality after 65 years in 2020 [22]. Also, there are gender-related differences in mental health issues, women are more predisposed to anxiety-mood disorders while men have more frequently externalizing-substance disorders [23] and are more predisposed to self-harm [22]. According to studies, rate of mental health disorders is raising and even in 2019 it was

already 7.2 % of the EU population over 15 years old, who reported chronic depression, whereas in 2021 14% of all hospital beds were psychiatric care beds in EU hospitals [22].

According to CDC more than every fifth US resident had mental illness. And every twenty-fifth US adult had serious mental diseases, including schizophrenia, bipolar disorder, or major depression [24]. Whereas prior to COVID-19 pandemic rate of mental health problems was experienced by every sixth EU citizen according to WHO [25].

In agreement with the report, published in Lancet in 2022, the rate of age-standardised disability-adjusted life-years (DALYS) were highest in Australasia, Tropical Latin America, and high-income North America. Globally, the age-standardised DALY rate for mental disorders per 100 000 population was 1426,5 among males and 1703,3 among females. The higher incidence among mental disorders in 2019 is depression with DALY rate 37,3%, anxiety disorders 22,9% and schizophrenia 12,2% [13].

Thus, depressive disorder is one of the most frequent mental health problem world wide, it includes several conditions, like unipolar major depression, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, and depressive disorder due to another medical condition. The most disabling illness is Major depressive disorder (MDD) with incidence from 2 to 21% it has serious impact in morbidity and mortality rate. It correlates with female gender and marital status [26]. Among all mental problems, depression and anxiety come out on top, even among teenagers. It is very important to assess the presence of a problem in a timely manner and provide timely assistance, given that these conditions can lead to serious disability and death via suicide.

Additional tool to analyze mental health issues is to estimate big pharma market. For example, EU Anti-Depressants drugs market size was \$3.12 bn in 2022 and it is estimated 4.64% growth from 2022 to 2030 up to \$4.48 bn in 2030 [27]. Whereas market size in North America was \$6.0 bn in 2019 with estimated 6.7% yearly growth. Also, according to market analysts data, global antidepressants market size was \$11.67 bn in 2019 with projected to grow up to \$18.29 bn by 2027 [28]. Now we faced some kind of psychopharmaceutics crisis, related to that fact, that depression investigations lie in between scientists, big pharma marketing, clinics, patients and regulatory agents. After FDA approval of advertising of these medications in 1997 [29], situation has worsened due to inappropriate information about medications effects, indications, effectiveness and side effects, that should be in the competence of a doctor and not relate to the marketing [30] [31] [32] [33]

It is important to note here, that the trends in the pharmacological market correspond to global statistics related to mental health. However, pharmaceutical campaigns and scientists pursue slightly different goals, and we may encounter overprescription of such serious drugs as antidepressants, which also have their dangers.

2. Antidepressant medication

MDD is the most frequent issues among mental health globally, but with appropriate treatment up to 80% might reduce their symptoms significantly [34]. There are several AD (antidepressants) groups, that might be used:

- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin/Norepinephrine Reuptake inhibitors (SNRIs)
- Atypical Antidepressants
- Serotonin Modulators
- Tricyclic Antidepressants (TCAs)
- Monoamine Oxidase Inhibitors (MAOIs)
- NMDA Antagonists

This medication vary by mechanism of actions, indications, contraindications and side effects. Though, the most frequent side effects include sexual dysfunction, drowsiness, weight gain, insomnia, anxiety, dizziness, headache, dry mouth, blurred vision, nausea, rash, and tremor also there could be hyperprolactinemia and hyponatremia [35].

SSRIs are usually first-line therapy for depression and their actions are related to enhancing and prolonging serotonergic neurotransmission by blocking reuptake of 5HT [36] [37]. Additional adverse effects related to SSRIs are sexual dysfunction, headache, QTc prolongation [38].

SNRIs are increasing postsynaptic receptors' stimulation by blocking serotonin and norepinephrine reuptake in the synapse with more affinity to norepinephrine especially in case of duloxetine, venlafaxine, and desvenlafaxine [39]. Additional side effects of this group include hypertension, headache, diaphoresis and bone resorption [40].

Atypical antidepressants have various mechanisms of action. Bupropion inhibits reuptake of dopamine and norepinephrine at the presynaptic cleft [41] as a serious side-effect, this medication can lead to seizures [42]. Agomelatine is an agonist of melatonin receptors and promotes dopamine and norepinephrine release due to antagonism to

serotonergic 5-HT_{2C} receptors [43]. Its side effects is hepatotoxicity. Other medication from this group is mirtazapine, that promotes release of norepinephrine into the synapse due to blocking alpha-2 adrenergic receptors on the cell bodies and nerve terminals also it is agonist of 5-HT receptor, that results in increasing norepinephrine and dopamine level in the brain's cortical regions [44]. Its side effects are sedation and weight gain [45].

Serotonin modulators inhibit serotonin reuptake and are agonist of 5-HT_{1A} receptor. However there some differences in mechanism of action inside this group. Also side effects may vary, for example, nefazodone may provoke acute hepatitis with cholestasis and variable degrees of centrilobular necrosis [46] whereas vilazodone and vortioxetine may induce diarrhea and nausea, correspondingly and trazodone – sedation and priapism [47].

TCA inhibits the reuptake of norepinephrine and serotonin at the presynaptic neuronal membrane. TCA thus can cause sedation and anticholinergic side effects, including dry mouth, urinary retention, constipation, QRS prolongation, seizures and orthostatic hypotension [48] [49]. MAOIs are first discovered AD. They inhibit the monoamine oxidase, that is enzyme responsible for catabolizing serotonin, norepinephrine, and dopamine. MAOIs are not recognized as the first-line treatment for depression because of the adverse effects and drug-drug interactions [50]. Side effects also include potential for serotonin syndrome and sexual dysfunction [51].

NMDA antagonists are used for depression treatment. The act is related to NMDA antagonism, that is connected to reducing of glutamate and gamma-aminobutyric acid (GABA) activity. Esketamine is a S-enantiomer of racemic ketamine, that is indicated in treatment-resistant depression. However, it has significant potential for misuse and dissociative or perceptual changes and sedation [52]. Other group members are dextromethorphan that is uncompetitive NMDA receptor antagonist and opioid σ receptor agonist and bupropion inhibits the uptake of dopamine and norepinephrine. This combination is fast and effective treatment for major depressive disorder with following side effects: dizziness, headache, somnolence, and dry mouth [53] [54].

Most contraindications for AD are related to between-groups interactions and also for patients with known hypersensitivities or taking other psychotropic medications. Also, some ECG abnormalities, liver problems and antibiotics prescriptions should be carefully analyzed in this case [34]. According to the literature review, toxicity is higher for TCAs and MAO inhibitors followed by venlafaxine, bupropion, and mirtazapine and is lower for

SSRIs. Among the selective serotonin reuptake inhibitors, citalopram and fluvoxamine appear to be associated with higher case fatality rates in overdose [55]. Also AD are used for self-poisoning attempts, so, patients conditions should be monitoring. Currently, the FDA has approved 7 groups of antidepressants, which have their own indications, contraindications and side effects. Obviously, this is quite a serious therapy that requires careful weighing of all the pros and cons both before prescribing therapy and before its cancellation.

Several tools might be used for monitoring AD therapy, including measurement of serum or plasma concentrations of antidepressants, then might be more reliable index than dosage. Also monitoring side effects is very important part of AD control [56]. Additionally several questionnaires might be used for that purpose, like Patient Health Questionnaire (PHQ-9) [57]; Hamilton Rating Scale for Depression (HDRS-17); Montgomery-Asberg Depression Rating Scale (MADRS) [58]. Despite this it is crucial to monitor adverse drug reactions, coexisting anxiety, or medical disorders at each visit as well as assess the response to therapy and consider augmenting or switching antidepressants in an inadequate response [34].

Discontinuation of AD therapy is decision, requires high expertise and also it is a complex process, due to several reasons. First of all, AD discontinuation is possible only when not only acute symptoms were cure, but when complete remission is achieved, otherwise, it will be high risk of relapse and reoccurrence of initial condition [59]. Also, it is important not to discontinue AD soon after acute episode, in case if some residuals symptoms remained, risk of relapse increases [60]. So, discontinuation of AD is possible in case of full remission and should be performed under medical doctor supervision. Evaluation of mental health status of the patient is possible not only via consulting but with additional tools like questionnaires, that help to assist patients' condition. The most commonly used are mentioned above, HAM-D and the Clinical Global Impressions-Severity and -Improvement scales (CGI-S and CGI-I, respectively) [61]. However, many different tools and questionnaires are used in studies and absence of one standard pool of assessment leads to high heterogeneity in study results. AD discontinuation is related to risks of relapse or recurrence and discontinuation symptoms. There are several somatic and psychologic symptoms related to so-called antidepressant withdrawal or discontinuation syndrome and might be AD-class-specific [61]. However, there are some similarities, including restlessness, trouble sleeping, unsteadiness, sweating, stomach problems, feeling an electric

shock in the head, mood changes, like low mood or feeling irritable, feeling of anxious or confused [62]. According to SR, provided by Davies J., and colleagues in 2019, withdrawal effects of AD were lasted (in heterogeneous populations) from 5 days up to 79 weeks [63].

There are no drug-specific protocols for AD discontinuation established. However, it is recommended to taper and discontinue AD slowly, regarding to AD type and patient condition [61]. Additional tools for support AD discontinuation are carefully examined recently, such as online controlling tools, psychoeducation, tools for health care practitioners assessments. Also, cognitive behavior therapy (CBT) and mindfulness-based behavior therapy (MBCT) that are lifestyle interventions related to mental health and stress-management are useful for AD discontinuation assessment [64] [65] [66] [67]

3. Lifestyle medicine

Lifestyle medicine (LM) is a branch of evidence-based healthcare emphasizing disease prevention over curative medicine [68]. Concept of lifestyle medicine was developed in 1989 by cardiologist Rippe J. and it implies integration of lifestyle medicine into modern practice with aim to prevent diseases by reduction of their risk factors or to support medical treatment [69]. According to the definition, LM is a branch of medicine which has as a goal to maintain optimal health and to prevent, treat and reverse chronic illness across all life stages. The health interventions used in lifestyle medicine include evidence based behavioral strategies, while considering equity and sustainability, to enhance self-management skills for optimizing nutrition, sleep hygiene, stress management, social connection, sexual health and fertility, physical activity and minimizing substance use and environmental exposures [7]. LM uses holistic approach, also it is evidence-based branch of medicine, so, treatment strategies, that used for patient's behavior changes are evidence-based. Also, it is important to mention, that LM provides doctor-patient partnership, that plays a key role of effectiveness of this strategy [69].

Lifestyle is effective methods due to uniting several tools, including science and knowledge about epidemiology and pathophysiology of chronic disease, LM practice skills, tools that LM can add for diagnosis and prescription and actions, that can help conventional medicine especially in relation to chronic diseases. Actions may include for example weight loss or quit smoking [70]. According to Egger C, 2016, the science of behavior change and the principles from this as espoused in the psychological literature, including, but not limited to, components of influence, motivational interviewing, the art of coaching, coaxing and

nudging patients from extrinsic to intrinsic motivation, and other processes to facilitate long-term change to healthy lifestyle behaviors [70]. Behavior change is a complex process, requiring several approaches, including education, 5 As (ask, assess, advise, agree, and assist) [71], understanding stages of change [72], that are: precontemplation, contemplation, preparation, action, maintenance. Motivational interviewing is one of the most useful tools for precontemplation, contemplation, and preparation stages of change. It is a patient-centered, collaborative counseling approach [73]. It is the process of engaging in an open-ended discussion with an individual to assess an individual's readiness to change with the goal of drawing upon the person's own desire and motivation to change, rather than the provider's motivation [74]. Motivation interview is different from other approaches to helping patients change in its focus on change talk [75] and includes engaging, focusing, evoking, planning. Additional useful tool is SMART goal settings, that is acronym of: specific, measurable, achievable, relevant, time-bound, evidence-based, strategic, and tailored to a patient, and it is a comprehensive patient-centered action plan for health behavior change [76], that might be integrated in the behavior change talk. It is complex but effective tool, that makes lifestyle medicine an effective measure for diseases prevention and accomplish treatment of different conditions.

4. Lifestyle medicine chapters and antidepressants

Lifestyle medicine quit is novel direction of evidence-based medicine, that improves health and overall well-being working with 8 main pillars, using behavior change techniques. It is important, to improve these pillars, including nutrition, physical activity, sleep hygiene, stress reduction, sexual health and fertility, social connections, minimizing substance use and environmental exposure, because, insufficiency of one of these pillars might be a risk factors of majority diseases. Thus, healthy lifestyle can prevent or at least accomplish diseases treatment. There are already several guidelines, that use lifestyle medicine recommendation for treatment and prevention chronic disease, including cardiovascular diseases, mental health, obesity and cancer [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [8] [9] [10].

Nutrition is one of the important chapters of lifestyle medicine, whereas inappropriate nutrition is a risk factors of several conditions, including obesity and cardiovascular disease risks, for example. It is known, that weight gain might be associated with AD therapy. For instance, for patients, who are treated with second generation antipsychotic drugs and with some mood stabilizers, TCAs. In the other hands, several

antidepressant and antipsychotic drugs do not cause weight gain and even may reduce it. However, monitoring weight might be important for these patient groups [94]. Additionally, according to Scheen A.J. in 2023, weight gain and increased insulin resistance might be associated with several antipsychotics, also author mentioned, that this population may also be predisposed to sedentary lifestyle and unhealthy diet. So, lifestyle measures should be performed in these cases [95]. To avoid life-threatening events, psychiatrists must pay attention to concomitant medications and individual factors underlying overweight and obesity [96]. In few studies, lifestyle intervention, including diet were described. For example, nutritional counselling was found to be effective for treating bulimia nervosa, with improvement maintained up to 3 months' follow-up. Authors also mentioned, that addition of fluoxetine may provide some benefits, but there might be some issues, related to discontinuation of this medication [97].

HP (especially ginseng, rhodiola rosea, ginkgo biloba, milk thistle) are associated with a significant risk of pharmacokinetic and pharmacodynamic interactions with psychotropic drugs. Because of the resulting complications and side effects, any decision to include a herbal supplement should be preceded by a detailed safety analysis with benefit and risk assessment [98]. Another initiative was described by Chmiel I. in 2022, he provided a case and literature review with possible effectiveness of ketogenic diet in therapy of bipolar affective disorder due to stimulation of mitochondria biogenesis, brain metabolism improvement, neuroprotection and oxidative stress reduction. However, author concluded, that this idea requires further investigations [99]. Also there were several cases, provided by Brogan K and colleagues, with using diet and supplements to help patients to discontinue AD [100] [101]. In majority of studies, supplement usage did not show enough evidence for further using these additives. Data from observational studies and randomized controlled trials (RCT) seem to point to their use for specific indications. For example folate, S-adenosylmethionine and eicosapentaenoic acid antidepressant effects were described, whereas zinc might be used for attention deficit hyperactivity disorder and vitamin B1 deficit is frequently found in alcohol abused patients [102]. Evidence, that selenium and eicosapentaenoic acid might be used for postnatal depression prevention is insufficient [103]. On the other hand, the daily intake of the food supplement based on S-adenosyl methionine and probiotic strains for a period of three months might be useful for patients with subthreshold depression subjects who are not eligible for antidepressant therapies, and patients suffering from mild-to-moderate depression who are not sensitive or cannot tolerate

conventional drugs [104]. Also, there was a pilot study, suggesting, that intake of omega-3 can be used with an antidepressant effect or as adjuvant therapy with some other medication for patients with Parkinson disease [105]. However, all this data requires further investigation. Especially due to the knowledge, that herbal supplements, like ginseng, rhodiola rosea, ginkgo biloba, milk thistle might be associated with significant risk of pharmacokinetic and pharmacodynamic interactions with psychotropic drugs [98].

In 2017 Catalá-López F. and colleagues performed meta-analysis and SR of RCTs regarding to the idea to compare pharmacological, psychological and complementary and alternative medicine (dietary therapy, fatty acids, amino acids, minerals, herbal therapy, homeopathy, and physical activity). They analyzed treatment response and all-cause discontinuation as primary outcomes, whereas secondary outcomes included discontinuation due to adverse events (tolerability), as well as serious adverse events and specific adverse events. Authors concluded, that behavioral therapy, stimulants and their combination showed the best profile of acceptability. Also, they mentioned, that efficacious pharmacological treatments were associated with harms (anorexia, weight loss and insomnia), without increasing of serious adverse events. Finally, authors concluded, that there was a lack of evidence for cognitive training, neurofeedback, antidepressants, antipsychotics, dietary therapy, fatty acids, and other complementary and alternative medicine mostly due to clinical and methodological heterogeneity, small sample sizes of trials, short-term follow-up [106].

Some psychopharmacological drugs may additionally change the nutritional habits of the patients in an unfavorable way leading to weight gain and obesity and the risk for further psychiatric problems [102].

Several medications, including SNRIs might be used for pain reduction. Interesting findings were provided by Morris M and colleagues in 1990, when two groups of regular male runners were compared. One group continued running, whereas the other group stopped running in the middle two weeks in 6 weeks study. According to questionnaires, depression symptoms were greater in the withdrawn than in the control group at the end of the second week of withdrawal and include anxiety, insomnia and feelings of being under strain were greater in the withdrawn group after both the first and second weeks of withdrawal [107]. In SR, provided by Kolber M.R. et al., 2021 exercise being the only intervention that demonstrated sustained benefit after the intervention ended [108]. Physical

activity effects should not be underestimated, but, however, it might be not enough for patients over 65 years old with a clinically significant depressive episode according to data, provided by Hidalgo J L-T. and colleagues, antidepressant treatment was superior in the medium term comparing to supervised physical exercise program, however, there were greater number of adverse effects in the medication group [109].

The current findings described here implicate a new direction for research, targeting the shared mechanisms underlying comorbid depression-CVD. This will guide the development of novel therapeutic strategies for the prevention and treatment of these stress-related pathologies, particularly within treatment-resistant populations [110].

In meta-analysis, with aim to compare efficacy and acceptability of treatments for depressive symptoms in cognitive impairment. In this study, 13,043 participants from 107 RCTs were included, involving 28 treatments and the discontinuation of antidepressants. Aerobic exercise, aripiprazole, behavioral training, electrical current stimulation, massage, music therapy and reminiscence therapy were significantly better than placebo. Among them cognitive stimulation therapy, electrical current stimulation and reminiscence therapy significantly outperformed the placebo. Additionally, no treatments showed a significantly higher risk than the placebo [111].

It is well-known, that insomnia is one of AD withdrawal effects, on the other hand, some ADs are used to improve sleep quality [112]. However, sleep hygiene is not the lifestyle intervention that is largely described in the literature. Most papers discussed it only in relation with AD side effects.

Stress management, namely MBCT, CBT are useful and effective tools for patients with depression and showed its effectiveness in several studies for patients with chronic pain, for example [113]. Also, there was a study that showed six-year outcome of CBT for prevention of recurrent depression, that showed significantly lower relapse rate comparing to clinical management 40% vs 90%, correspondingly [114]. Also, potential long-term effects of a mind-body intervention for women with major depressive disorder were showed in a pilot yoga intervention [115]. According to SR provided by Maund E. et al., CBT or MBCT can help patients discontinue AD without increasing the risk of relapse/recurrence, but this type of intervention requires additional resources [116].

AD might be used to cope with several sexual problems. In SR, provided by McMahon C.G. et al. in 2011, showed effectiveness and safety of SSRIs, tramadol, and dapoxetine treatment of men with premature ejaculation [117]. However, AD may provide sexual dysfunction. For example, there is data about possible dose-response relationship between SSRI exposure and persistent sexual adverse effects. There is limitation of treatment options for this condition and require further investigations [118]. There was a study related to antidepressant-induced sexual dysfunctions and different nutraceuticals that might improve situation comparing to placebo [119].

Several studies were performed to estimate risks of AD therapy and pregnancy. It is complex situation, concerning mothers'-and baby's health. The idea was to clarify if SSRI can provoke autism spectrum disorders in children. For that reason, two groups were compared: pregnant women who discontinued SSRI until 3 months before pregnancy; pregnant women who were exposed to SSRI during pregnancy; and pregnant women with maternal psychiatric disorder but no exposure to SSRI during pregnancy. There was no significant difference between the groups, however, tendency for increase was observed in the 1st group. Authors conclude that further studies are required [120]. Park M. and colleagues, 2021 mentioned, that prenatal AD exposure was selectively associated with worse anxious behaviors and physical independence at kindergarten age, with no effects on other developmental domains [121]. On the other hand, Bliddal M. and al., 2023 said, that: "while SSRI exposure was associated with increased risk in the children, this risk may be driven at least partly by underlying severity of maternal illness or other confounding factors" [122].

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Mental and substance use disorders are becoming leading causes of disability globally. Frequency of substance use disorder started to raise since 1990 years [13] and the most prevalent are alcohol and drugs use disorder with prevalent opioid misuse [123]. Anxiety disorders that can be comorbid with alcoholism include panic disorder, social phobia, obsessive compulsive disorder, generalized anxiety disorder, and posttraumatic stress disorder. Also, anxiety disorders may be co-incident with alcohol abuse. Treatment of an anxiety disorder can rarely, if ever, be expected to cure alcoholism. However, more

research is needed in this area [124]. Interesting study was performed by Strong D.R. and colleagues in 2012, patients completed a stress-challenge task before receiving their first dose of buprenorphine, that resulted in successful transition to early abstinence, and lower rates of opiate use during the initial 3 months of buprenorphine treatment across antidepressant and placebo groups [125].

Minimizing environmental exposures in patients with AD therapy is not widely described lifestyle medicine chapter. However, there is one study, that suppose a positive effect of well-being therapy for a treatment of depressive disorder. This strategy was manualized by Fava G in 2016 and includes environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, positive relations with others, and balance of psychic forces. This type of intervention was effective according to several RCT [126]. Additionally, according to the study provided by Madsen I.E.H., and colleagues, 2015, level of burnout predicted antidepressant treatment with a stronger association in men than women. There was no effect-modification by the examined work environment factors, though a sensitivity analysis indicated a possible stronger association in women of lower occupational position [127].

Social connections are very important to patients who suffers from depression. However, according to Lund et al., 2018, there is no universal definition of social connectedness, it is considered an umbrella term that generally includes the following components: social support, social networks, absence of social isolation and loneliness [128]. The majority of studies, regardless of type of support, showed that social support is a protective factor for both depressive symptoms and disorders [129]. It is known, that Parkinson disease might be associate with depression and sometimes requires AD therapy. Depressive symptoms during "off" periods (i.e., at nadirs of drug levels) may be relatively intractable and warrant patient and family education. So, family education and support might be an important part of patients' treatment [130]. According to Young N.S., and colleagues there is one mechanism of antidepressant drugs is that they promote more positive social interactions, due to increasing serotonin function and decreasing aggressive and irritable behavior and increasing agreeable behavior [131].

In study, provided by Dingle G.A. et al., 2021, social group interventions were examined as a way to manage mild to moderate depression according to patients aim to discontinue antidepressant use. SR data showed, that social group interventions are an

effective way to manage mild to moderate depression symptoms in a variety of populations. This approach may also help to prevent relapse among patients tapering off antidepressant medication [132].

5. Online tools in counselling and patients' assessment

In addition to all mentioned above, we should not underestimate existing technology progress. Technology also provides tools that can be used in clinical practice. New devices help to access, track and monitor many parameters, like steps amount, blood pressure, heart rate, temperature, saturation, blood glucose, physical activity levels, duration of sleep phases and ect. So now we get into the era of new devices and developments called mHealth or health care and public health practices supported by mobile devices and other advances in telemetry [70]. However, these tools require further evaluation. There are several mental health apps, that might be used in field of mental health, some of them has up-to-date information on prevention, assessment and treatment and even self-help. It might improve patients health and well-being and make medical staff life easier [133]. According to scoping review, provided by Lukmanji S. and coll. in 2017, they analyzed current situation corresponding to "Online tools for individuals with depression and neurologic conditions". There were only 4 online tools, including 2 web-based self-management programs for patients with migraine or multiple sclerosis and depression. The other 2 were mobile apps for patients with Parkinson disease or traumatic brain injury and depression. No online tools were found for epilepsy [134]. Roberts L.W. and colleagues in 2018 analyzed existing mobile and connected technologies in advancing psychiatric diagnosis, author mentioned that: "we have not seen mobile and connected technologies fundamentally transform routine diagnosis of psychiatric disease or other aspects of clinical psychiatric care. And thus far, with limited exceptions, we have not also seen strong efforts at scientific and clinical investigation of the new tests and new tools that mobile technology makes possible" [135]. In systematic review (SR), which analyzed tools for evaluating the content, efficacy, and usability of mobile health apps according to the consensus-based standards for the selection of health measurement instruments, authors concluded, that the most validated tools are The Health Information Technology Usability Evaluation Scale and the Measurement Scales for Perceived Usefulness and Perceived Ease of Use, but with focus on usability. However, existing tools, apps are widespread, but requires further validation [136].

Mobile health applications may help in health promotion for large patients groups and some of them are successfully implemented for example in cardiology, according to

results of TEXTMEDS study, that is Text Messages to Improve Medication Adherence and Secondary Prevention After Acute Coronary Syndrome [137] [138]. Similarly, Haase J et al., mentioned that mobile applications could improve medication adherence, and patient will consume medications as prescribed [139]. Ideally it might be combination of traditional treatment followed by mobile application [140]. So, on the one hand, lifestyle medicine education and positive psychology interventions have been shown to improve wellbeing among the public [141]. On the other hand, face-to-face coaching is effective tool in delivering health and wellbeing programs, that we faced especially during COVID-19 pandemic [142]. Digital health counselling may provide support independently on localization of expert and patient, that may have additional positive economic effect [143]. Also, development new treatment strategies for mental health issues might have additional economic benefits [144]. In addition, the current problem of careful withdrawal of antidepressants is a complex problem that requires an integrated approach, and perhaps the use of remote lifestyle medicine consultations may be an advantage for such patients, especially in situation, when regular monitoring is required. This approach requires further investigations.

To sum up existing literature, mental health issues are the most frequent conditions in modern society, especially depression and anxiety. These conditions should be controlled due to high risks of disability and suicides. However, AD medications are often underestimated and over-prescribed, whereas process of AD discontinuation is complex and might be unsuccessful, and very often results in relapse and AD re-administration. Lifestyle medicine with its holistic approach might improve this situation. However, the most studied is mental health practice, though lifestyle medicine has other chapters, that may improve overall health and well-being. The most useful tools in lifestyle medicine are behavior change techniques, including motivational interview and SMART goals setting. But these other methods, despite CBT and MBCT, have not been studied in relation to this topic. Additionally, according to studies, there are no standard tools, that are used for control patients' condition during the process of AD tapering and discontinuation. This assessment requires further investigation. Additionally, digital health technologies, counselling and mobile applications become often used tools supporting different interventions, because it provide additional monitoring of the patient condition. However, these tools also require further investigation and validation. Uniting lifestyle medicine techniques, lifestyle medicine holistic approach, digital health technologies that accomplish process of AD

discontinuation might be a novel method of evidence-based support patients with indication to stop their AD medication. Thus, it requires further investigations.

2. Aims – Significance

The aim of this study was to check existing lifestyle medicine approach in support patients with discontinuation of antidepressants therapy, provide working scheme of this support, using lifestyle medicine intervention; perform 1,5-year support program with multiply lifestyle interventions for patient, who taper and discontinue antidepressant therapy and present it as a Case Study; access effectiveness, reliability and reproducibility of this type of intervention.

To achieve these goals, the following tasks have been performed:

1. Scoping review conduction for clarifying current investigations related to this topic;
2. Case study formation;
3. Checking lifestyle medicine intervention, that accomplishes antidepressants discontinuation during case study;
4. Clarifying initial condition and condition during and after protocol to evaluate withdrawal antidepressants effects;
5. Summarizing results;
6. Discussion of the Case Study results, comparing results with existing ones in literature, Scoping Review results.

3. Scoping Review

For clarifying current state of the art about lifestyle medicine interventions, that are used for antidepressants discontinuation, scoping review was conducted.

3.1. Methods

Scoping review was performed according to “*The Joanna Briggs Institute Reviewers’ Manual 2015*” [6] and Cochrane library guide, provided by Dr. Andrea C. Tricco and Kafayat Oboirien [145] Prior to scoping review conduction, preliminary research was performed. In several databases, including PubMed Central, Embase, Cochrane Library, Web of Science, and Wiley Online Library, there were no results received according to this topic.

3.2. Objective and research question

The aim of this Scoping Review is to summarize current data and evidences for applying lifestyle interventions for antidepressants discontinuation to reduce possible withdrawal effects, arising in connection with cessation of drug therapy. Therefore, the research question included clarifying interaction between all types of lifestyle interventions and withdrawal effects of antidepressants during discontinuation of the therapy. So, all possible links (including correlation, prevalence of a specific pattern, etc.) between all lifestyle medicine pillars, namely: nutrition, physical activity, sleep hygiene, stress management, decreasing of substance use, sexual health and fertility, social connections and reduction of environmental exposure and different types of withdrawal antidepressants’ assessment were investigated in this review.

3.3. Eligibility criteria

3.3.1. Inclusion criteria

Inclusion or eligibility criteria implied all papers with full text and abstracts, that include lifestyle intervention, that include few or at least one lifestyle medicine pillars and assessment of antidepressants discontinuation withdrawal symptoms were included in the review. So, studies, that provided information about these parameters together (lifestyle medicine and antidepressants discontinuation) and have methodological design were eligible

All metrics for lifestyle intervention and measurements of antidepressants discontinuation are provided in Table 1 Eligibility criteria and was performed using PICOS.

Table 1 Eligibility criteria

Inclusion criteria:		Exclusion:	
P	>18 years Both men and women	P	Animal studies Non-adults
I	Any lifestyle intervention separately or together Physical activity Sleep hygiene Nutrition/ diet Stress management Sexual health Social connections Substance use Environmental exposure	I	No lifestyle intervention No physical activity No sleep hygiene No nutrition/ diet No stress management No sexual health No social connections No substance use No environmental exposure
O	Main outcome: stress, anxiety reduction, reduction of withdrawal effect	O	No measurements for stress and anxiety

3.3.2. Exclusion criteria

Exclusion criteria are listed below:

- Animals' studies;
- Studies of non-adults;
- Studies without any lifestyle intervention;
- Studies without antidepressants discontinuation;
- Studies without any assessment of withdrawal symptoms of antidepressants discontinuation (Table 1 Eligibility criteria).

3.4. Search strategy

Three steps searching strategy were used during this scoping review conduction, according to *JBIR Manual* [6]. All steps were performed by one reviewer (Elizaveta Kuznetsova).

During the first step MEDLINE/Pubmed and Cochrane database were checked without any filters by language, publication date, or study design. No relevant data were found during this phase. Also, additional sources were checked manually ad idem outcome.

Figure 2 Final Search Strategy for MEDLINE

(lifestyle interventions or lifestyle medicine or lifestyle medicine interventions or healthy habits or healthy habits formation or healthy lifestyle or well-being therapy or WBT or physical activity or exercise or fitness or nutrition or diet or healthy eating or Mediterranean diet or med diet or keto diet or sleep hygiene or therapy for insomnia or stress management or mindfulness or MBSR or cognitive behavior therapy or CBT or behavior therapy or mental health or mind-body intervention or cognitive therapy or sexual health or sexual dysfunction therapy or social connections or Community referral or Social group interventions or Social prescribing or (minimizing and (substance or Amphetamine or methamphetamine or ketamine or alcohol) and (use or misuse or abuse)) or smoking cessation or minimizing environmental exposure) AND (antidepressants or antidepressants medication or SSRI or temazepam or zopiclone or zolpidem or Risperidone or Duloxetine or mirtazapine or psychotropic drugs or Antipsychotic; or Antipsychotique or antidepressant agents or Antidepressant drugs or Benzodiazepine agonists or discontinuation syndrome or treatment discontinuation)

Figure 1 Final Search Strategy for COCHRANE

("lifestyle interventions" or "lifestyle medicine" or "lifestyle medicine interventions" or "healthy habits" or "healthy habits formation" or "healthy lifestyle" or "well-being therapy" or "WBT" or "physical activity" or "exercise" or "fitness" or "nutrition" or "diet" or "healthy eating" or "Mediterranean diet" or "med diet" or "keto diet" or "sleep hygiene" or "therapy for insomnia" or "stress management" or "mindfulness" or "MBSR" or "cognitive behavior therapy" or "CBT" or "behavior therapy" or "mental health" or "mind-body intervention" or "cognitive therapy" or "sexual health" or "sexual dysfunction therapy" or "social connections" or "Community referral" or "Social group interventions" or "Social prescribing" or (minimizing and (substance or Amphetamine or methamphetamine or ketamine or alcohol) and (use or misuse or abuse)) or "smoking cessation" or "minimizing environmental exposure") AND (antidepressants or "antidepressants medication" or SSRI or temazepam or zopiclone or zolpidem or Risperidone or Duloxetine or mirtazapine or "psychotropic drugs" or Antipsychotic or Antipsychotique or "antidepressant agents" or "Antidepressant drugs" or "Benzodiazepine agonists" or "discontinuation syndrome" or "treatment discontinuation") AND (discontinuation or "stop medication" or "stop therapy")

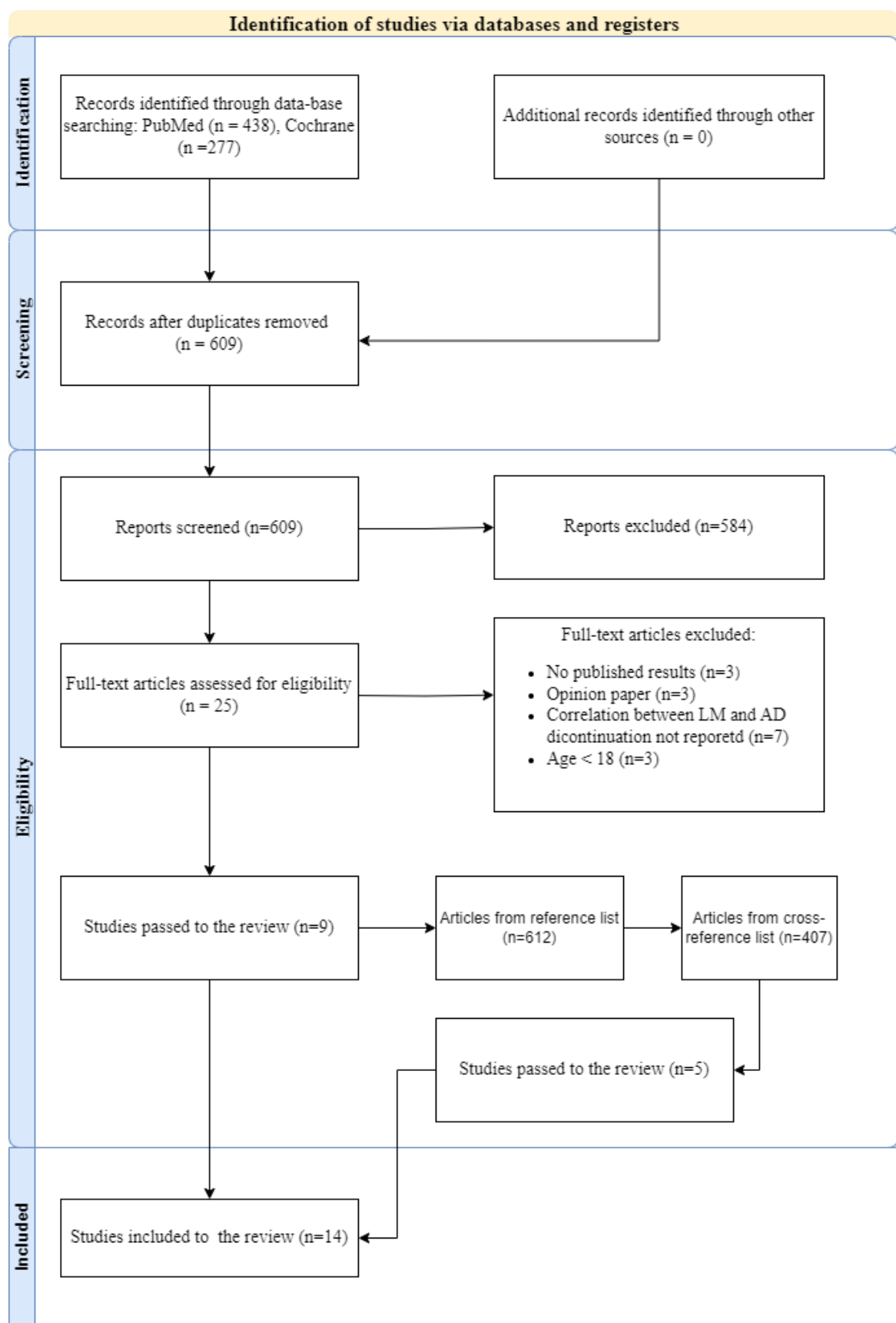
At the second step, search in MEDLINE/PubMed, Cochrane was performed with all identified keywords. All papers published before 30.05.2024 were included in search strategy. Searching algorithm is allocated in Figure 2 Final Search Strategy for MEDLINE and in Figure 1 Final Search Strategy for COCHRANE

Screening algorithm was adopted to requirements of each database. Duplicates were removed from the search by removing titles with the same PMID and then according to duplicated titles with using VBA in Excel. After removing duplicates, papers were screened for eligibility criteria. Inclusion and exclusion criteria are mentioned above.

Third step was performed after identification all eligible papers, by performing references lists screening for additional eligible papers.

Most papers were excluding based on information, provided in titles and abstracts. In cases, where an article was not provided, full text was examined for eligibility criteria. Full text was obtained in all eligible articles. Additionally, 612 papers were screened during analysis of reference lists of eligible papers and 407 papers through cross-reference list. All searching strategy could be found in (Figure 3 PRISMA Flow Diagram for the Scoping Review Process. After all analyses, there were 14 papers, included in the current review.

Figure 3 PRISMA Flow Diagram for the Scoping Review Process.



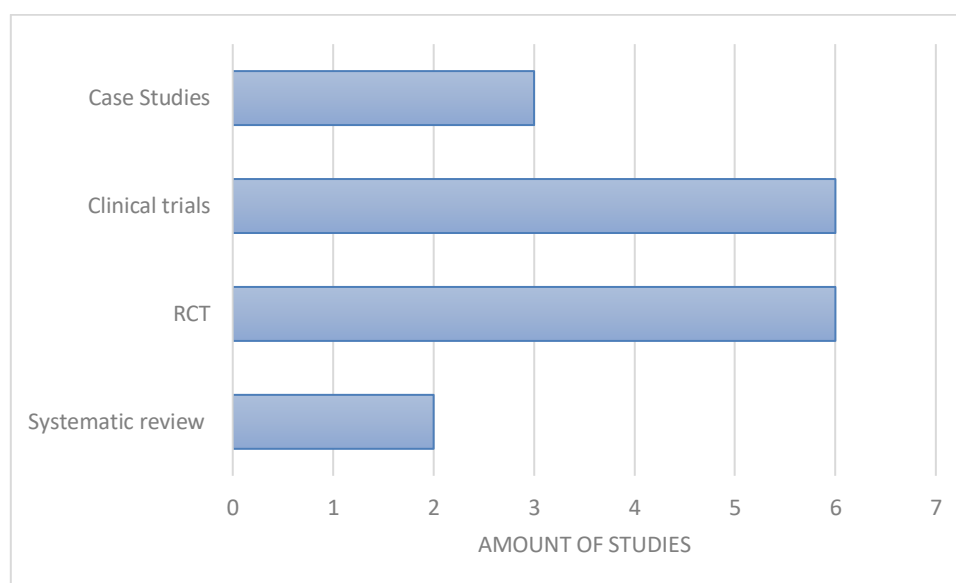
3.5. Extraction of the results

- Following information was analyzed for papers, included in the review:
- Information about the main author year of publication;
- Type of the study;
- Aims of the study;
- Main characteristics and inclusion/exclusion criteria of the study population;
- Type of lifestyle intervention;
- Methods of evaluation antidepressants discontinuation;
- Main results and its relation to the research question.

3.6. Presentation of the results

After searching there were 14 papers that meet eligibility criteria for final observation, including 2 SR were included in current scoping review (Figure 4 Type of included papers). In 2 SR there were 6 papers, that will be described below.

Figure 4 Type of included papers

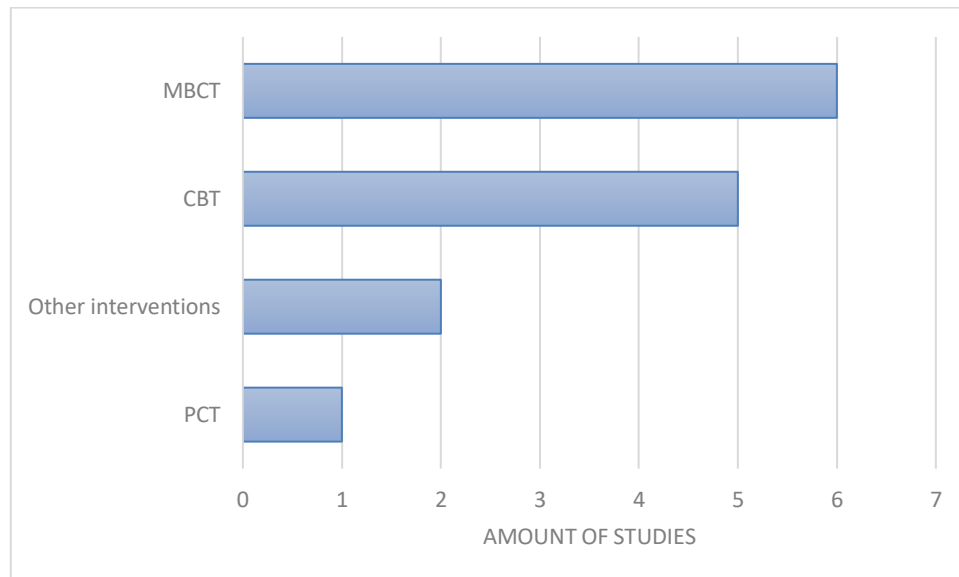


The main study characteristics and findings of the included studies are presented in the Table 4 Data extraction table(Appendix 3).

Number of participants varies from 1 (in Case Reports) to 424 in RCTs, but were relatively small in Clinical trials with participants number below 100 in most of them. All studies include lifestyle intervention and AD tapering and discontinuation. The most frequent lifestyle interventions were CBT [146] [64] [65] [147] [66] or MBCT [148] [149]

[150] [151] [152] [67] and other interventions [153] [100] [101] that accomplish antidepressants discontinuation. Interventions distribution is presented in the Figure 5 Type of Lifestyle Intervention

Figure 5 Type of Lifestyle Intervention



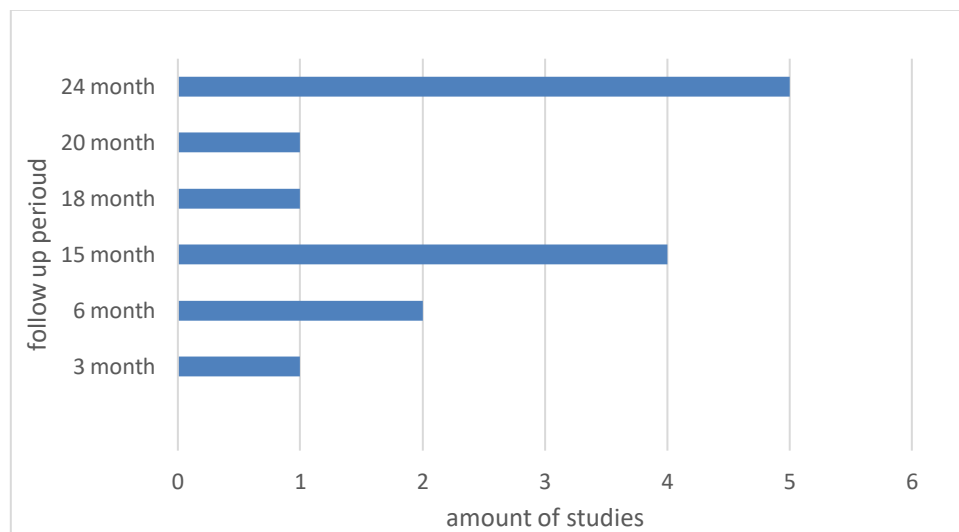
In most of the studies lifestyle intervention was compared with continuation of AD or with other support like clinical management. Additionally, it is important to mention, that there were 2 case reports [100] [101] and 1 case series [66]. In 2 case reports, there were different lifestyle intervention, comparing with all other studies: diet, physical activity and meditation [100] [101].

Study designs were not similar, there were comparison between CBT+AD discontinuation versus CBT + mADM [146] that was similar to study with MBCT intervention [148] [150]. Also, similar design with other conclusions were published later by the same authors group (based on previously performed RCT), a percent of patients with full/partial/ or without discontinuation of AD was estimated as well as incidence of relapse in MBCT plus full AD discontinuation group [149]. Also, times to relapse were evaluated in studies comparing MBCT-TS vs mADM [150] [151] [67], whereas in study provided by Segal Z.V., Bieling P., et al., 2010, MBCT-TS were compared with mADM and PLA+ clin [152]. Also, additional to CBT strategies were compared to CM support in 2 similar studies [64] [65], whereas in study, performed in 1998 by Fava G.A., Rafanelli C. And colleagues, additional comparison to initial measurements was performed with further relapse percent evaluation [65]. In 2 other studies effects of CBT, accomplishing AD discontinuation were

estimated without comparison [147] [66]. Moreover, there were 2 case reports, that describe different clinical cases but with similar interventions, that include diet, exercises, meditation and psychological support [100] [101].

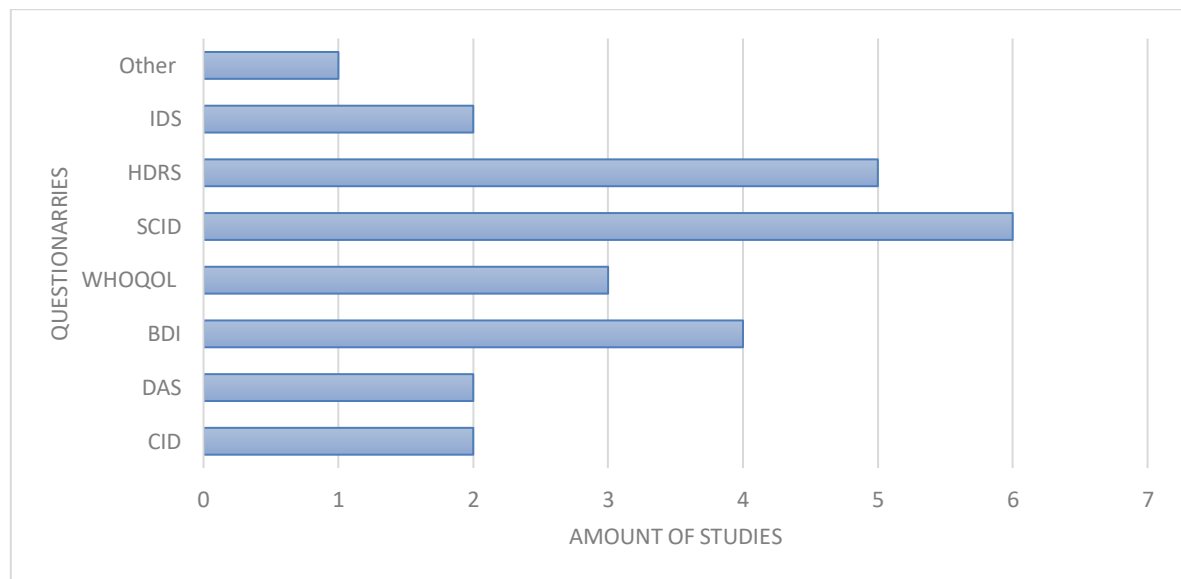
All studies, with exception of 2 case reports (where this information is NA and clinical evaluation were used) analyzed results via questionnaires and follow up ranged from 3 to 24 months. With usual follow up period 15 – 24 months (Figure 6 Follow up period).

Figure 6 Follow up period



DSM IV classification or its previous versions [154] were used for diagnosis. Also, patients in the studies mainly met following inclusion criteria: previously experienced at least two or three depressive episodes with current remission or recovery on antidepressants therapy (AD therapy at least during 6 months). Furthermore, questionnaires were used to estimate intervention results, risks or relapse/reoccurrence depression or other problems, related to AD discontinuation. Totally 32 different questionnaires were used in all eligible studies. The most frequently used questionnaires were: SCID, HDRS, BDI and WHOQOL, whereas other 25 questionnaires and tools were used only ones. It shows quite high heterogeneity during evaluation process (Figure 7 Estimation result of intervention)

Figure 7 Estimation result of intervention



3.7. Discussion

Aim of this review was to summarize current data on existing lifestyle interventions, that facilitates AD discontinuation reduce possible withdrawal effects and is effective enough to prevent relapse/re-occurrence initial condition. The main findings are following: (i) there are not enough data corresponding to this topic, due to the fact, that CBT and MBCT are the most studied methos, whereas other lifestyle interventions described only in two Case Reports [100] [101]; (ii) inclusions and exclusion criteria were similar in all studies, whereas methodology, tools were results estimation and follow up period between studies vary significantly.

Idea of methodology of cost-effective support of AD discontinuation is actual and amount of studies, regarding to this topic, raises gradually. Methodology differences as well as difference in questionnaires and follow up period results in absence of confident, if CBT or MBCT is hundred percent working method. However, in most studies, advantages of this methods were shown: according to Fava G.A. and colleagues, CBT were beneficial to CM by lower level of residual symptoms and relapse rates that was 25% vs 80% in CM group [64] [65]. Similar results were obtained in case of MBCT therapy [67], as well as relapse rate were lower in MBCT group 47%, comparing to 60% in mADM group [66], but relapse rate is quite high even in case of MBCT group. In study, provided by Huijbers MJ, Wentink C in 2020, in MBCT patients who completely discontinue AD therapy, relapse rate was 50%

during within 6 month [148]. However, time to relapse doesn't differ between MBCT and mADM groups [151]. Controversially to that in the study, provided by Huijbers MJ and colleagues in 2026, it was concluded, that an increased risk of relapse/recurrence in patients withdrawing from mADM after MBCT [148]. However, it is important to mention, that effect of intervention corresponds to management effectiveness of acute phase of initial condition [152]. Moreover, no difference was found during comparison CBT+AD discontinuation and CBT without AD discontinuation, in study, provided by Schmidt NB and Wollaway-Bickel K. in 2002 [146]. Also positive relation was found between CBT and AD discontinuation in 12 women, who were planning pregnancy [147] and in Case series for 8 patients, who discontinue their therapy [66], the result remains stable during 6 and 3 month follow up period, correspondingly.

CBT and MBCT protocols are standard and did not significantly differ between studies, with the exception of support sessions during follow up period [152] [67] [66]. However, other types of lifestyle interventions described only in 3 papers [65] [100] [101]. Fava G.A. and colleagues, used combination of CBT of residual symptoms of major depression with lifestyle modification advice and well-being therapy sessions [65]. Other two studies were Case Reports, that used individual approach with various lifestyle intervention, including diet, yoga, meditation, physical exercises and psychological support [100] [101] with quite long, 24 months, follow up period. Certainly, there is more individualized successful approach, that was described in both cases. However, it seems, like multifaceted intervention gave additional support, that helps discontinue AD with low relapse risks.

Furthermore, it is important to mention, that eligibility criteria for patients were similar in all studies, with the exception of Case Reports, where patients had more serious initial conditions, but this type of study estimates more personalized approach with possibility of more often symptoms evaluation, comparing with RCTs protocols. The problem is (despite difference in intervention methods or comparison methods) the results evaluation. Tools and questionnaires for studies results evaluation varied significantly from study to study (Figure 7 Estimation result of intervention and Table 4 Data extraction table).

3.8. Brief conclusion

There are no big trials in the literature about the existence of lifestyle program, supporting AD discontinuation. According to data, the most used methods are CBT and MBCT and there are the most effective in combination with antidepressants discontinuation. It was mentioned that they are time-consuming, but cost-effective methods [155]

Positive thing is that similar patient's group was studied. However, lack of standardized methods for results evaluation is a thing that might be studied more. What's more, tools for prognosis evaluation for this patient's group, like mentioned by Segal Z.V. and colleagues, effectiveness of acute phase treatment [152], might be useful for choosing duration of support program and follow up period.

Other lifestyle interventions are described only in 2 Case Reports, which showed positive effect and effectiveness of this approach. However, this data is not enough to change current situation in AD discontinuation supportive methods. Holistic approach such as using other lifestyle medicine pillars for reducing withdrawal effects for antidepressants discontinuation requires further investigation.

4. Case Study

A possible lifestyle medicine approach is shown in this case study. It is a tool, that might be used to support patients with discontinuation of antidepressants therapy.

Abstract

Background. A 37-year-old female with a long history of AD therapy due to mild severe anxiety and mild depression wanted to taper and discontinue her AD therapy because of her desire to plan new pregnancy. Due to long term history of antidepressants therapy, there was a possibility in occurrence of withdrawal syndrome, that may result in unsuccessful attempt of AD discontinuation, whereas continuation of AD therapy might influence on pregnancy and fetus (depending on medication type). That's why the idea to use additional support during AD discontinuation appeared and was realized during 1,5 years to accomplish AD tapering and discontinuation with 3 months follow up period.

Summary. A patient with initial anxiety who had additional risk factors for anxiety and depression, such as initial health condition (she has been diagnosed with thyroid cancer), family conditions (second marriage with alcohol abused person and two kids), stressful work, that requires high concentration, attention and many responsibilities. History of long-term AD therapy and two previous unsuccessful attempts to stop AD therapy, then resulted in AD re-admission. First of all, this third attempt had serious underlying cause to plan new pregnancy. Secondly, AD tapering and discontinuation was performed in stable family and social conditions. Additionally, it was a personalized plan of discontinuation, that took into account current patient condition, and changing of her condition in relation with her life situation, including illnesses and stressful work. And finally, this attempt was accomplished with multiply lifestyle medicine interventions with improving healthy habits in fields of stress management, sleep hygiene, diet, physical activity, social connections and reducing, environmental exposures. Moreover, it is important to mention, that all lifestyle interventions were performed via online video-consultations and online support. She does not experience any adverse symptoms and do not use any medications during 3 months after AD discontinuation.

Conclusion. This study is a successful example of how complex holistic and personalized approach can support a patient and accomplish AD tapering and discontinuation. Also, it is the example of successful healthy habits introducing into intensive and stressful megapolis life of an office worker, a mother of two kids, and a wife

of alcohol-abused person and cancer survival. She successfully stopped taking her AD medication, started doing regular physical activity and exercises. She followed healthy diet and used sleep hygiene to improve her sleep quality and became experienced in many tools for stress management. Additionally, she improved her social connections and reduced environmental exposures. This case is an evidence of importance of multiply lifestyle interventions, that could support such kind of patients who taper and stop their AD therapy. This process may become more effective and safer despite of it being time consuming.

4.1.Introduction

During last decades, depression and other conditions require antidepressants therapy. Whereas, up to 30-50% prescriptions for long-term antidepressants therapy are not evidence-based [2]. Another problem is that AD discontinuation is not a process that could be easily performed. There are several problems related to withdrawal symptoms. These symptoms might be severe and include dizziness, fatigue, insomnia, gastro-intestinal problems and even suicidality [156]. One more problem is a possibility to relapse or reoccurrence of depression or other condition that requires AD re-initiation [157]. On the other hands, our society do not have comfort conditions for medical workers and patients' tool to tapering and discontinuation of AD. There are two problems corresponding to this topic despite lack of knowledge, there are also lack of time and necessity for psychologist and absence of holistic approach [158]. Lifestyle medicine is a branch of evidence medicine that uses holistic approach for non-communicable diseases prevention and well-being. Lifestyle medicine includes few chapters that are so important for mental health. The main chapter for this topic is stress management, but sleep hygiene, social connections, nutrition, physical activity, sexual health and minimizing substance use are equally important to a person with mental health issues [<https://eulm.org/what-is-lifestyle-medicine>]. According to multiply studies, the most popular intervention for mental health problems, especially related to depression, is CBT [146] [116]. Behavioral therapy is evidence-based approach that is included in NICE guidelines. However, it is important to mention that sometimes it is not enough and CBT is not a holistic approach. Another popular method that accomplishes AD discontinuation in different studies are MBSR, that might be used successfully for some patients [152] [150]. Unfortunately, data from studies is controversial somehow. Most of studies agree in benefits from CBT and MBSR for being good tools to accomplish AD tapering, but in some studies it was mentioned, that it might not be enough to prevent relapse or recurrent depression [148]

Unfortunately, there are only several case studies where other lifestyle medicine approaches were successfully used [100] [101]. However, these case studies were published just recently and there are numerous studies about CBT and antidepressants discontinuation. It means that safe antidepressants discontinuation is a relevant topic that requires novel evidence-based on a holistic approach.

4.2.Patient information

History of life:

- Date of birth 22.11.1985
- High education 2002-2007 in industrial and civil engineering field
- Additional education 2010-2014 - psychologist, psychology teacher
- Additional education 2017-2018 general-purpose chef, pastry chef, cooking courses
- Additional every-year professional education courses

Social history:

- 1 st marriage 2006-2014
- Caesarian section 04.11.2006
- Work changes
 - 2005-2006
 - 2008-2009
 - 2009-2011
- “Natural” baby birth 20.11.2014
- Stressful condition due to c-r diagnosis 30.11.2015
- 2 nd marriage 2017 – present
- Work changes
 - 2017-2018
 - 2018-2021
- 2018-2019 husband’s alcohol abuse
- 9-11.2019 – husband treatment
- New work: 2021-present: stable job in a large company that brings personal and financial satisfaction with good health conditions (medical insurance, psychological support, canteen, fitness club, swimming pool)

Medical history

- Height 170 cm, weight 65 kg
- No history of allergy
- No substance abuse, no smoking, no alcohol
- No family history of mental health problems
- Patient's father died from heart attack at age before 45
- History of illnesses:
- No tuberculosis, or other diseases like hepatitis B or C, or HIV
- Operations:
- appendectomy in childhood
- thyroidectomy due to c-r 30.11.2015
- No history of gastritis, cholelithiasis or urolithiasis disease
- No heart problems, neurological problems or traumas

Medication on the first visit (22.12.22) levothyroxine 125 mg/daily, vit D and Ca supplements, Venlafaxine 150 mg/day

History of AD therapy is presented in Table 2 History of AD therapy. Firstly, AD was prescribed to the patient in 2012 due to anxiety.

Table 2 History of AD therapy

Diagnosis	Therapy, group	Duration	Comments
Anxiety	SSRIs	2012-2014	Acute stop due to pregnancy
Cyclothymia, F34.0	TCAs + BZN	2015-2018	Stressful condition due to c-r diagnosis
Worsening anxiety	Acute stop due patient wish	02.2018	Stressful situation ended due to change the work
Worsening anxiety and depression	SNRIs	09.2019	Stressful situation in personal life
	Gradually AD discontinuation	22.12.2022-01.2024	With LM support
	No therapy – Nj LM intervention	02.2024-20.05.2024	Follow up

History of illness:

We had initial consultation with the patient many years prior to the current case. She consulted EK as a GP and cardiologist due to some conditions like acute viral infections, flu and etc. Current situation started in 2015, when patient experienced heart discomfort, palpitations, unstable heart rate, fatigue, sweating, irritation and anxiety. Her ECG and standard blood test were without any abnormalities; therefore, patient was recommended to check her TSH level, that was elevated 7,66 mIU/L (0,27-4,2) and papillary thyroid carcinoma was diagnosed after ultrasound checking. EK remotely followed patient during pre-operation preparation and recommend hospital and a specialist for thyroidectomy. The operation was successful, without any complications, and no radioactive iodine therapy or other type of radiation/chemotherapy was required. After surgery the patient was consulted with a psychiatrist and diagnosis Cyclothymia, **F34.0** was established. Cyclothymic Disorder is a DSM-V [159], diagnosis assigned to individuals who experience mood cycling over a two years period, but have not met the diagnostic criteria for Bipolar I, Bipolar II, or Depressive disorder. AD medication (TCAs) and benzodiazepines (as a pill in the pocket) were prescribed for the long-term period.

Due to personal reasons patient stopped her AD medication without tapering in 2018. That period was stressful due to work and family situation. The situation became better after the patient quitted her job. New AD prescription was in September 2019 due to worsening patient condition, that symptomatically results in anxiety, fatigue, poor sleep and irritation. Partially it was associated with stressful situation in family and partially with job-related stress. SNSIs were prescribed, and initial dose of 75 mg of venlafaxine was raised up to 150 md daily plus possible BZN as a pill in the pocket.

In December 2021 the patient found stable work according to her initial specialization with good salary and employee-friendly environment, that includes medical insurance, gym and pool in the main building, canteen and psychological support. Due to stable condition and anxiety level reduction, patient consulted with her psychiatrist and they developed a plan of AD tapering and further discontinuation. Patient is aware about following withdrawal symptoms, that may exist during venlafaxine discontinuation: irritability, nausea, feeling dizzy, vomiting, nightmares, headache, and/or paresthesias (prickling, tingling sensation on the skin) [160]. Therefore additionally, patient asked EK for online lifestyle mentoring during the process of AD discontinuation, because of her wish

to make the process safer and plan new pregnancy. There were no financial interactions between EK and patients and Case Study started after patient's written consent.

4.3.Clinical findings

During 1,5 years Case Study patient had 5 checkups, that included general blood test, standard biochemistry test, thyroid hormones evaluation, ECG. Additional tests were performed during and after illnesses, in case it was necessary due to clinical conditions. Checkups were performed at the initial of the Case Study in December 2022, in April 2023 with additional lipid level checking (it was required for running competition), in December 2023 9 due to seria of illnesses) and in May 2024 (follow up the AD discontinuation). No serious abnormalities due to analysis and ECG examination were found.

During these 1,5 years, there were several illnesses, that reduced AD tapering and required additional counselling and sometimes rehabilitation:

- 3.02.2023 COVID-19
- 13.02.2023-19.02.2023 Streptococcal infection, antibiotic therapy
- 27.02.2023-3.03.2023 Dysbiosis due to antibiotic therapy, probiotics prescription.

After illnesses blood test evaluation showed normalization of all parameters, including WBC.

- 10.11.2023 – Misdiagnosed otitis media (after swimming aqua park visiting), treatment initiation after culture results. Local therapy was prescribed in the 20th of November
- 5.12.2023 – COVID-19
- 9.12.2023 – Otitis media, that required antibiotic therapy
- 29.12.2023 – 7.01.2024 Onset new flu infection

After these illnesses in December 2023 additional vitamin supplementation were admitted (included magnum and vitamins group B for 3 weeks) and probiotics after antibiotic therapy during 3 weeks.

After illnesses blood test evaluation showed normalization of all parameters, including WBC.

- For evaluating such parameters as HR, sleep duration and steps amount, patient used smart watches and shared results with EK.
- Bioimpedance parameters were analyzed prior and during 1,5 year Case Study period.

4.4.Interventions

Additionally to checkups and bioimpedance several validated questionnaires were used to evaluate initial situation. The same questionnaires were used during AD tapering prior to complete AD discontinuation and during follow up period:

- HADS scale for anxiety and depression evaluation [161] [162]. The HADS is a self-report rating scale of 14 items on a 4-point Likert scale (range 0–3). It is designed to measure anxiety and depression (7 items for each subscale). The total score is the sum of the 14 items, and for each subscale the score is the sum of the respective seven items (ranging from 0–21) [163] [164]
- SATED questionnaire for sleep quality evaluation [165] [166], this scale assesses five key dimensions of sleep that have been consistently associated with health outcomes and include Satisfaction with sleep; Alertness during waking hours; Timing of sleep; Sleep Efficiency; and Sleep Duration [167] [168]
- EQ-5D-3Q quality of life [169], that is a self-classifier, that enables the respondent to classify their health according to five dimensions, including mobility, self-care, usual activities, pain/discomfort and anxiety/depression, also there is 20-cm vertical scale with endpoints of ‘best imaginable health state’ set at 100 and ‘worst imaginable health state’ set at 0 [170] [171]
- Self-reports about stress level, diet and self-performed schedule and daily routine were used additionally to questionnaires.

There are 8 well known lifestyle medicine chapters. Only 6 of them were used for lifestyle intervention in the current Case Study: sleep hygiene, stress management, physical activity, nutrition, social connections and reducing environmental exposures. Sexual health was not discussed due to patient’s wish and there was no need for minimizing substance use, because patient did not use any substances, including cigarettes and alcohol.

It is important to mention, that prior to AD discontinuation patient participated in 8 weeks MBSR training in autumn 2022 and she had additional education as a psychologist, psychology teacher, that gave additional advantages in this clinical case.

Lifestyle intervention included online meeting on a regular basis with motivation interviewing of the patient and creating an achievable goal with using SMART goal system.

SMART system is an evidence-based tool, it is the way to health behavior change, with specific, measurable, achievable, relevant, and time-bound goals [172] [76]

Generally, there were 12 big 1-1,5h online video meeting during this period, when lifestyle medicine chapters were discussed and SMART goals were established, with regular every 1–2-week support via messenger and 3 additional follow up meetings after AD discontinuation. SMART goal was related to physical activity, sleep hygiene, stress reduction (Figure 8 Timeline).

4.5.Outcomes

During **first session**, that lasted 1,5 h, we discussed lifestyle medicine pillars, current situation and patients' motivation to taper antidepressants. Patient shared a plan with me, has been developed together with her psychiatrist. We discussed her schedule in general and patient realized, that the main problem for her is poor sleep quality (Figure 8 Timeline).

Prior to the next meeting she filled questionnaires and wrote a diary, how many hours did she sleep, and amount was around 5h. On the **1h meeting 2** we discussed sleep hygiene, and factors that may influence it, including process of melatonin synthesis. And it was concluded that short 20 min walk in the middle of the day might improve the situation. Motivation interview was performed and SMART 1 goal for the next 2 weeks was established by the patient in the end of the session.

Between the sessions patient got sick and her sleep quality became worse. However, she continued small daily walks in the middle of the day during her lunch break. We did not have meeting with video during this period, but communicated via messenger. SMART 2 was established 19.02.23 during **1h 3rd meeting** and it was related to sleep hygiene. We additionally analyzed patient's schedule and importance to wake up very early to take her medication for thyroid and it is additional resource for the patient to relax while other family is still sleeping SMART 2 goal was related to sleep hygiene and daily routine that included preparation to sleep and for the new working day beforehand, continue 20 min everyday

walking and using the same routine at the weekends during 1 month. We had short support conversation in between sessions via messenger.

SMART 3 was established during **1h meeting 4**, when patient shared that her sleep improved and she had been sleeping regularly during 7 h, and her steps amount raised up to 11000 steps per day, while it was about 5000 in the beginning of the Case Study. Goal for the SMART 3 was stress reduction. We discussed possible tools that might be used during office stress. The patient was interested in breathing techniques. We looked through patients' schedule and found a possibility to try some breathing techniques during lunch break or in the acute situation using room for relaxation in the office any time when it is necessary. During next week the patient got familiarized with several breathing techniques and used the most comfortable for her. Moreover, we discussed how she would count stress situations during her working day, and when it is important to her to make a short pause for breathing exercise. This SMART 3 goal was also 1 month duration. In one-month the patient became so well trained in breathing techniques, that she could perform it even in the elevator in standing position.

SMART 4 goal was established during **1h meeting 5** patient shared the idea to participate in 10 km running competition. The idea was not related to any awards, just to the desire to try this running distance. SMART 4 goal was related to the training plan. During next week we discussed HR that might be the best for the patient, keeping in mind her initial condition with thyroid cancer. Additionally, she was advised to find running trainer and we also discussed hydration, nutrition and best training time. Here, it is important to mention that the patient visited fitness center in her office and started exercising regularly (twice per week with fitness instructor in the gym) since spring 2023. Also during preparation to the running competition, we have every-week sessions. Finally, 20.05.23 patient successfully run 10 km without any discomfort and without any health problems after that.

During our **1h meeting 6** in June we discussed and summarized fitness results and discussed importance to exercise regularly. No SMART goals were established that time. Also, we discussed possibility to visit swimming pool as additional method of training and relaxation.

Next **1h meeting 7** was in in the beginning of Julye and related to nutrition, without any smart goals. It was just a discussion about nutrition importance, different type of diet and brain food. Also, we discussed hydration importance, after this session patient was

consulted via dietitians during 1,5 months and started to count calories and improve her diet, also started her dinner earlier, around 17-18.

There were some kind of relapse in lifestyle intervention during summer months (July and August 2023), but patient worked with dietitian that period. We were communicating via messenger. However, patient successfully continued taper her AD. And by the beginning of the autumn, it was less than 75 mg dose.

During next meeting in September, EK realized that the patient started to train so actively (7 days during week) and became exhausted and stressed. Therefore, during **1h meeting 8** we worked on her schedule to reduce number of exercises.

During **1h meeting 9** we discussed importance of social connections, without any SMART goal. The patient is active sociable person, with warm relationships in her family.

During **1h meeting 10** the patient told me about her sleep worsening, and the level of anxiety increase due to work-related stress. During our meeting we discussed that the patient stopped doing her sleeping routine, 20 min walking and meditation. EK reminded the patient about lifestyle medicine pillars (sleep hygiene, stress management). The patient realized that the easiest of all might be returning to sleep hygiene routine. On the next week meeting she added breathing techniques.

In November 2023 patient got weak, and she was sick during 1,5 months. During her illness we discussed sleeping routine and there were no lifestyle intervention and AD tapering during that period. After recovery EK provided rehabilitation program with gradual return to work, and gradual increase of physical activity level, sleep hygiene and stress management and vitamins supplementation. It was performed during **1h meeting 11**.

During **1h meeting 12** we discussed reduction to environmental exposure, without establishing any SMART goals.

In January the patient performed a check up and got results without any abnormalities. And patient successfully stopped her AD medication.

After AD discontinuation conversation became less intensive and was only once per month. Therefore, we had 3 follow up meetings and final checkup in May 2024. There was follow up period with additional test evaluation. She mentioned about anxiety episodes due

to terrorist attack in Moscow. We discussed possible techniques for relaxation, that might help. The situation improved according to the next follow up meeting.

During follow up meeting in May the patient commented that she had training sessions regularly 2-3 times per week, had healthy diet, regular walks, 7h sleep and breathing techniques upon the request. Also, she mentioned, that she collected bottles plastic covers and wasted it separately in the office and find this situation as an additional meditation process.

4.6.Patient Perspectives

The patient with a history of AD and BZN therapy since 2012 year and successfully stop her AD medication in 2024. It is important to mention that she had 2 unsuccessful attempts in the past in 2014 and 2018 years. But that time discontinuation was performed without tapering and any additional support. It resulted in worsening symptoms of anxiety and re-admission od AD therapy in 2015 and 2019 years, correspondingly.

This attempt was accomplished by tapering plan via psychiatrist and support with lifestyle mentoring, provided by EK during this period and follow up.

There were 12 motivation interviewing sessions, 4 SMART goals establishment with successful achieving that goals and 3 follow up sections. Additional sessions were between the main sections every 1-2 weeks.

As a result, the patient started to exercise regularly, and even participated in 10 km running competition. She improved her sleep quality and sleep duration raised from 5 to 7 h without any medication. Also, she became familiar with multiply stress reduction techniques, especially breathing techniques, that she could use in stressful conditions. The patient improved her diet and as a result of all mentioned above, she improved her physical and mental capacity, that we could see via questionnaire results (Table 3 Questionaries results), bioimpedance results, she lost 5 kg and raised her muscular mass (Table 5 Bioimpedance results) and in that fact that she is coping with her everyday life without AD medications.

Table 3 Questionaries results

Questionary	12.2022	02.2023	05.2023	11.2023	02.2024	05.2024
HADS	A-3; D-2	A-3, D-11	A-1, D-1	A-12, D-5	A-1, D-1	A-2, D-1
SATED	4	8	9		9	8
EQ-5D-3Q	70	30-46-50	95	53	89	97

4.7. Brief conclusion

Based on this case, AD discontinuation should be performed under personalized tapering plan with additional support via using lifestyle medicine. This holistic approach helps to cope with different withdrawal symptoms. Also, regular follow up creates safer conditions and provides trusting partnerships between patient and the expert.

This Case Study might be used for future programs developing and might be used even when symptoms are not curable via only medications.

Lifestyle intervention is an evidence-based approach. However, it is a time-consuming method, that might provide stable results.

It is important to personalized patients' needs and patients' pace of AD discontinuation for more stable results.

Nevertheless, in current case there were 2 unsuccessful attempts with re-initiation of AD therapy within 1 year, therefore we need to prolong follow up period for at least to 12 months after AD discontinuation.

Nonetheless, this approach is perspective and requires further investigations, especially possible combination of using lifestyle medicine techniques with other evidence-based techniques for AD discontinuation, such as CBT and MBCT.

5. Overall results

To achieve aims of this study two general studies were performed: Scoping Review was conducted to review current literature and to understand what interventions appropriate evidence has and might be used for AD tapering and discontinuation. Also, this review was performed with an idea to investigate, what chapters of lifestyle medicine were used according to this topic. The second part of the work presents results of a Case Study, where multiply lifestyle interventions were used to support patients during tapering and AD discontinuation to reduce possible withdrawal effects.

Scoping Review were performed after analyzing two databases, PubMed and Cochrane. 1734 articles founded according to this topic (Figure 3 PRISMA Flow Diagram for the Scoping Review Process.). However, only 14 were eligible for final evaluation. Among those 14, there were 2 SR (6 papers from that reviews were used at final evaluation) and 2 interesting Case Reports (Figure 4 Type of included papers). CBT and MBCT were the most often used interventions, that accomplished AD tapering and discontinuation. Patients groups and their inclusion criteria as well as methodology of interventions were similar. Nonetheless, comparison groups and follow up duration as well as tools and questionnaires for outcome measurements varied between different studies, that provided heterogenous methodology and differences in results. According to the most of the studies, CBT and MBCT are preferable comparing to clinical management for AD discontinuation. Also, it is important to mention that there were 2 Case Reports and one Case Seria, that were included in this review (Table 4 Data extraction table). Comparing to other studies, in these two Case Reports, different lifestyle interventions were used: diet, physical activity and meditation. And this complex approach showed good outcomes [100] [101].

Corresponding to described Case Reports, in our Case Study also provided successful AD discontinuation, that was accomplished by multiply lifestyle interventions, including diet, physical activity, stress management, sleep hygiene, social connections and reduction of environmental exposure. It was a case with 1,5 year duration, including 3 months of follow up period. Lifestyle intervention program was performed online and personalized according to the patients' needs and current situation in life. SMART goals were established during intervention and additional counselling via messenger were performed once, twice or weekly between each month general sessions when it was necessary (Figure 8 Timeline).

Patient tapered and discontinued AD in comfortable pace and AD therapy was stopped from 01.2024. Additionally, she improved her life quality, that we can see according to the questionnaires' results (Table 3 Questionnaires results). Her rates according to HADS scale is very low, sleep duration and sleep quality significantly improved (7 h, while it was 5h in the beginning) and SATED results are 8 comparing to 4, that was at the initial point of our study. Also, according to EQ-5D-3Q quality of life questionnaire, patient got 97 out of 100, comparing to initial 70 and 30 after diseases in the beginning of our study.

Additionally, it is important to pay attention to her bioimpedance results, via regular training and healthy diet, she improved her physical capacity thus she participated in 10 km running competition. According to bioimpedance measurements (Table 5 Bioimpedance results), her muscular mass raised and fat mass decreased as well as weight. During the study she lost 5 kg and her weight become stable 60 kg at the end of our study.

As for stress management, according to patient's comments, she managed to use breathing techniques each time when she needed it, even in an elevator. Also, she was training how to use breathing techniques as a preventive measure for basic stress reduction. So, she feels the moment when to use breathing before stress level became too high. Finally, she collects bottles plastic covers and finds it as a meditative process. Unfortunately, it is not a measurable result, but it is the evidence of successful realization of environmental chapter of lifestyle medicine.

6. Overall discussion

Initially, AD withdrawal effect was poor described in literature in some case studies, as a dizziness, lightheadedness, insomnia, fatigue, anxiety/agitation, nausea, headache, and sensory disturbance [173], or FINISH that is Flu-like symptoms, Insomnia, Nausea, Imbalance, Sensory disturbances, and Hyperarousal (anxiety/agitation) [174] or other somatic symptoms, including myalgias, arthralgias, parkinsonism, and electric like shocks [175]. According to literature it may appeared after AD discontinuation and last from few days to 2-4 weeks [174] [176] [63]. However, recent data showed, that these symptoms may last up to 1 year or even longer [63]. Likewise, recent data focused on the topic of possibilities and safer ways to discontinue AD therapy [177] [178] [179]. Due to withdrawal syndrome and re-occurrence of initial depression or anxiety, rate of relapse and AD therapy re-initiation is pretty high [180] [181]. At the same time, long-term therapy is not indicated

for all patients, and has its own side effects, such as weight gain, sleep problems, sexual dysfunction and even gastrointestinal bleeding, also risks of fragilis increases and falls in the elderly, additional risks of stroke and hyponatraemia as well as emotional blunting and low self confidence among all age groups [182] [183] [184]. Besides, in some cases AD therapy may be overprescribed [180]. And then a patient and a doctor may face “AD discontinuation syndrome” later, for example, in case of pregnancy. Not all AD can be used during this period and we have controversial data regarding this problem [147] [185] [186] [187] [188]. So, this is a fairly relevant topic. Even economic effectiveness of AD discontinuation was counted [180]. Although, AD discontinuation is feasible task, both medical doctors and patients faced many problems during this process, related to the lack of knowledge what symptoms might appear and how to support patients during this period. Additionally, AD discontinuation requires long follow up period for relapse prevention. According to conducted scoping review data, follow up period ranges from 3 to 24 months, with favorable 24 months follow up period (Figure 6 Follow up period), that was described in 35% of included studies, 15 months follow up was described in 28% whereas 6 months follow up in 14% of included studies (Figure 6 Follow up period). The longest follow ups were also performed in case studies [100] [101], whereas in our 1,5-year study we have only 3 months follow up by this moment. However, we are planning to continue follow up, especially due to that fact, that re-initiation of AD therapy for our patient happened twice during her medical history regarding returning initial symptoms after 1 year after AD discontinuation during two previous attempts. There is no doubt, that AD discontinuation should be performed gradually, with preceding AD tapering [189]. At the same time, according to our scoping review data, AD tapering and discontinuation process is not personalized, and usually it is 3 to 6 months period before complete discontinuation of therapy. In our case study, this process was personalized considering the patient's personal circumstances (including the dose reduction process slowed down during the occurrence of various colds or other events, such as training for a running competition) and stretched over time up to a one-year period. That was comfortable pace according to patient's self-reports. During our case study patient experienced some withdrawal symptoms, including increasing anxiety rates and even some depressive symptoms. Usually, it was related to illness and some stressful conditions at work. Patient mentioned later, that it was important for her to feel that she could control the process. It is somehow similar to the strategy that is shown in two other case reports, included in our scoping review [100] [101].

According to the data from our scoping review, the most studied among non-pharmacological interventions are evidence-based techniques such as CBT [146] [64] [65] [147] [66] and MBCT [148] [149] [150] [151] [152] [67], that was performed in the majority of included studies 35% and 42% correspondingly. CBT is a well-known and well-studied psychotherapeutic method, developed by Beck A.T. in 1960^s, that is focused on the interplay between thoughts, feelings, and behaviors and might be implemented for various psychiatric disorders [190]. MBCT is a type of mindfulness-based intervention as well as MBSR. MBSR is Mindfulness-Based Stress Reduction technique that was developed and implemented by Kabat-Zinn in 1974 [191]. MBCT is a combination of cognitive therapeutic techniques and mindfulness strategies that might be used for various mental health disorders [192]. CBT and MCBT protocol are standard and did not vary significantly between included studies despite differences in follow up period supportive sessions [152] [67] [66]. CBT intervention usually consists of 10 or 12 weekly sessions with usual 1-2 h duration, whereas MCBT included 8 weekly sessions, lasting 2 to 2,5 h. In clinical cases, included in our scoping review, there were no such interventions as CBT or MBCT, but there were some psychological support and meditation [100] [101]. It is important to mention, that in our case study patient had experience in MBSR, because she passed 8-weeks standard MBSR training course in autumn 2022 prior to participation in our program of AD tapering and discontinuation. Surely, this experience influenced the overall process positively, especially when we saw huge progress in mastering relaxation techniques, breathing techniques and stress reduction during SMART 3 in our case study.

Conforming to studies included in our scoping review, CBT and MBCT are in most cases effective supportive techniques for AD tapering and discontinuation. In SR, conducted by Maund E., Stuart B., et al in 2019, authors concluded, that in studies, where there are comparative supportive techniques for AD discontinuation it is important to have an alternative discontinuation procedure, usual care, or clinical management, but not placebo [116]. In 5 studies, eligible for our scoping review (from this SR), it was described that MBCT or CBT methods were preferable to mADP or clinical management. So, authors concluded, that this type of therapy can help patients discontinue antidepressants without increasing the risk of relapse/recurrence, but it is support, that requires resources and more scalable interventions with psychological support are needed [116]. In the second SR, provided by Van Leeuwen E. and co-authors in 2021, different approaches were analyzed: discontinuation combined with high-intensity psychological intervention versus

continuation of long-term antidepressants and discontinuation with a minimal intervention versus usual care [2]. Authors mentioned very low-certainty evidence of preventive cognitive therapy or MBCT resulted in successful discontinuation from 40% to 75%, absence of control groups data as well as in studies evaluated minimal usual care via usual intervention [2]. There were three eligible studies for our scoping review, among which we found two duplicates from Maund E., Stuart B. SR [116]. According to the third DRD study, included in Van Leeuwen E. SR, AD alone was not superior to PCT + tapering AD in terms of the risk of relapse or recurrence $p=0,502$. However, adding PCT to AD resulted in a 41% relative risk reduction compared with AD alone $p=0,026$ [153]. Despite this SR conclusions, it is important to line out the results, provided by Segal Z.V., Bieling P. et al in 2010, that effectiveness of AD discontinuation process is corresponding to acute phase treatment achievements [152]. Therefore, it might be important to use some relapse risk stratification prior to perform any program for AD discontinuation, but now there is not enough sufficient tool for that.

As it was mentioned above, CBT and MBCT are the most used and described methods among all in literature. Other lifestyle chapters were just occasionally met and there are only 3 papers in our scoping review, where other interventions are described [65], [100] [101]. Fava G.A. and co-authors described using combination of CBT of residual symptoms of major depression with lifestyle modification advice and well-being therapy sessions might be favorable for this patients' group [65] and Brogan K. and colleagues described other chapters of lifestyle interventions as nutrition, physical activity, meditation and yoga in two clinical cases in 2019 and 2020 years [100] [101]. Both authors noted effectiveness of such approach.

According to definition, Lifestyle Medicine is a branch of medicine which has as a goal to maintain optimal health and to prevent, treat and reverse a chronic illness across all life stages. The health interventions used in lifestyle medicine include evidence based behavioral strategies, while considering equity and sustainability, to enhance self-management skills for optimizing nutrition, sleep hygiene, stress management, social connection, sexual health and fertility, physical activity and minimizing substance use and environmental exposures [7]. The use of this evidence-based holistic approach has already been proven to be effective in a number of studies in different patients groups and is already being used in clinical guidelines [8] [9] [10]. Lifestyle medicine is useful in huge variety of conditions from fragile prevention in elderly [193] to improvement physical capacity in

hemodialysis patients [194]. Also, lifestyle intervention is a favorable technique for many psychological conditions including PTSD, loss and grief or stress management in every-day life [195] or helps to cope with substance use disorder [196] [197]. In our case study only 6 chapters out of 8 have been worked out. There was no need to include substance use chapter in our lifestyle interventions, due to absence of such problem for our patient. One more chapter that wasn't used during our case is sexual health, that is very important part of our lifestyle, that also plays role in overall and psychological well-being [198]. However, the patient was not ready to discuss this chapter during our case study, that was normal to the society she belongs to. However, she supposed to discuss this topic later during further follow up. In our case study patient showed significant improvement of her condition in most mentioned chapters. Her sleep quality and sleep duration were improved increased from 5 to 7 hours and SATED questionnaire results become 8 instead of initial 4. Additionally, patient learned how to cope with stress in her everyday life and even how to prevent high stress levels. She became familiar with several breathing and meditation techniques and we saw additional improvement according to HADS scale. Initial A score (for anxiety) was 3 with episode of high score - 12 due to stressful related-to work conditions (in 11.2023) and 2 points in the end of our case study. Also, initial D score (for depression) was 2 at the beginning, raised up to 11 due to illness in first months of our study (02.2023) and turned into 2 points at the end of our study. It is important to mention physical activity improvement, that started from increasing daily steps amount from 5000 to 11000 steps daily during just few months, that ends up with 10 km running competition. The patient is in maintaining physical activity level 3 times per week including gym and swimming pool. Additional benefits patient got after improving her diet from working with dietitian, that resulted in bioimpedance results improvement as well. We can see gradual weight loss which stabilized at 60 kg level, that was not initial aim of our patient. Muscular mass was increased and fat mass decreased, that is complex result of physical activity and diet changes in patient's lifestyle (Table 5 Bioimpedance results). Finally, we can see improvement in overall life quality satisfaction according to EQ-5D-3Q results, that were 70% over maximum 100% in the beginning, dropped to 30% out of 100% after illnesses (02.2023) and results in 97% out of 100% in the end of our study (Table 3 Questionnaires results). Similar chapters were used in case reports, included in our scoping review [100] [101], but there were no questionnaires mentioned. As for other studies, that were eligible for our scoping review, there was no strict tool that was used for outcome evaluation, therefore this part remains highly heterogenous. The most often used questionnaires were SCID, HDRS, BDI and WHOQOL. But overall

number of different tools that was used is 32. So, 25 questionnaires and tools were used only ones (Figure 7 Estimation result of intervention). SATED, HADS and EQ-5D-3Q that we used in our study are validated questionnaires, translated into many languages. Therefore, some standardizes assessment of AD discontinuation is certainly needed for future studies.

Summarizing all-above information, it is important to mention, that AD tapering and discontinuation is a complex process, that requires gradual and under-control tapering of the AD. It might be beneficial to perform some clarifying of initial acute-phase treatment effectiveness for further risk stratification. Prolong follow up of these patients shouldn't be underestimated as well as possible effective additional support. CBT and MBCT and other lifestyle medicine chapters might be effective and even beneficial strategy for this patients' groups. However, standardization methods for assessment effectiveness of antidepressant withdrawal are necessary as well as further research on this pressing issue.

7. Overall conclusions

During this study, current literature was analyzed. The highest evidence and studied techniques, that support AD tapering and discontinuation are CBT and MBCT. There were just several data, where other chapters of lifestyle medicine were evaluated, it was two case studies, provided by one author. In this Case Study nutrition, physical activity and meditation were used successfully together with psychological support [100] [101].

In our Case Study AD were tapered and successfully discontinued and the process was accomplished via multiply lifestyle interventions with 3 months follow up period. Overall duration of Case Study was 1,5 years (from 12.2022 to 05.2024).

6 lifestyle chapters were discussed and implemented during the Case Study and included: nutrition, physical activity, stress reduction, sleep hygiene, social connections and reducing environmental exposures.

During the lifestyle intervention, patient condition improved and AD were successfully tapered and discontinued. Besides that, the patient improved her sleep quality from 5 to 7 h, raised her physical activity level and she trains regularly 3 times per week, her bioimpedance characteristics became better (her muscular mass raised, whereas fat mass decreased, she lost 5 kg and weight stabilized at 60 kg). Patient even participated in running competition. Additionally, patient became familiar with stress management techniques,

especially breathing techniques, that she can apply according to request. She has been trained to understand how to use breathing technique as a preventive measure as well. We can see these improvements in questionnaires and bioimpedance results (Table 3 Questionnaires results, Table 5 Bioimpedance results). So, we can conclude, that this complex support program helped the patient to achieve her goals, to get stable results and to discontinue her AD medication.

Though, this program is successful, it is also time-consuming, that requires team work, including fitness trainer, nutrition specialist, psychiatrist, lifestyle mentor, who can coordinate all processes and preferably GP. Also, it is important to mention that this program was personalized according to the patients' needs and current situation in life.

There might be some obstacles in performing studies due to their design. It might be hard to design work according to personalized patients' needs, and it might be a problem to conduct RCT according to this topic, or study design might be very complex. So, observational studies are likely to be a tool to raise amount of evidence of this type of intervention. Additionally, it is not simple to prognose economic effectiveness of such kind of intervention. But lifestyle intervention is a tool for many diseases prevention, though it will be beneficial to implement lifestyle intervention anyway, due to that fact, that disease prevention is always more effective than disease treatment.

Thus, selected methods have been used to support different patients' groups for huge variety of health issues. Using our successful experience we can recommend our program for counselling and support of patients with antidepressants discontinuation for further investigation. Considering the potential of this program to be included in future recommendations after a sufficient period of observation.

8. Strengths & Weaknesses of this work

The great strength of this study is that lifestyle medicine intervention was used in real life setting and with individualized approach. Combination of individual plan of AD tapering and discontinuation that was accomplished by LM intervention is also a novel approach that makes this study unique. Team work, that includes a psychiatrist, a GP, an LM mentor, a running coach and a fitness trainer and a dietitian that gave additional benefits to the patient. Long support period and long follow up also make this complex intervention safer and provides more stable results.

Individualized approach and team work is a milestone of current work: all interventions were adapted according to patients' needs and current life situation. It was possible due to the fact that EK combined GP and mentoring skills that help to follow patients' health conditions at the same time.

Lifestyle intervention was performed via online video counselling and messenger as a between-sessions support. Online counselling was comfortable due to possibility to perform it when it is needed and in comfortable conditions without necessity to visit mentor's office. Also, online counselling was possible to perform even during patients' illnesses or re-scheduled easily, when it was needed.

Besides, complex lifestyle intervention was performed during this study. According to literature, such complex approach, that uses 6 lifestyle medicine chapters has not been performed before.

So, this study provides an idea of a novel concept to support patients who want to taper and discontinue their AD medication.

In terms of a patient control and evaluation patients' symptoms there were several limitations: firstly, due to the absence of such types of studies; secondly, the case study started prior to the Scoping Review conduction and initially it wasn't supposed to become a Case Study. This fact seriously limited tools that were used for patient condition assessment. Also, CBT or MBCT were not used as possible additional support method. So, using this evidence-based method for additional support for AD discontinuation may improve this program in future. Also, we plan to continue patient's follow-up for 12 months.

Additional possible weaknesses of this work concern it being time consuming, needs for team work and individualized regimen, that might be hard in organization and for RCT conduction in future due to a complex design.

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Appendix 1: Bioethics Approval



University of Thessaly
Intradepartmental Master of Science in Lifestyle Medicine
Internal Ethics Committee

Trikala:17/04/2024
Protocol Number:17/04/2024-02

Approval of research entitled: Lifestyle medicine vs withdrawal antidepressants' effect. A Case Study

Scientist responsible – supervisor: Prof. Giorgos K. Sakkas
Institution: University of Thessaly
Department: MSc in Lifestyle Medicine

Main researcher – student: Elizaveta Kurnetsova MD, PhD
Institution: University of Thessaly
Department: MSc in Lifestyle Medicine

The proposed research relates to a:

Research grant ☐ Postgraduate thesis ☒ Independent research ☐

Contact phone: Αφαίρεση προσωπικών δεδομένων (Υπηρεσία Βιβλιοθήκης &
Contact email: Πληροφόρησης Πανεπιστημίου Θεσσαλίας)

The Internal Ethics Committee (IEC) of the Intradepartmental Master of Science in Lifestyle Medicine, University of Thessaly, examined the proposal in its 17/04/2024 meeting and approves the implementation of the proposed research.

The Chair of the IEC – MSc in Lifestyle Medicine
Prof. Giorgos K. Sakkas

Appendix 2: Consent Form

Informed consent form for participation in a research study Информированное согласие для участия в исследовании

1. Title of the study/ Название исследования

"Multiply lifestyle intervention vs withdrawal effects of antidepressants' discontinuation. A Case Study".

Использование лайфстайл медицины для борьбы с синдромом отмены при прекращении терапии антидепрессантами.

2. Aim of the Study/ Цель исследования

The aim of this study is to promote multiply lifestyle intervention via mentoring program through regular video online consultation for a person, who gradually stops antidepressant therapy. The idea is, that lifestyle intervention with improvement of sleep quality, stress management, physical activity, proper nutrition, sexual health and social connections, working with addictions will help to reduce possible anxiety due to antidepressants discontinuation. Also, this intervention will provide working tools for future life.

Цель данного исследования провести программу по лайфстайл медицине, используя программу менторства посредством регулярных видео консультаций участника, который постепенно прекращает прием антидепрессантов. Идея заключается в том, что лайфстайл медицина улучшит качество сна, будет включать работу со стрессом, физической активностью, правильным питанием, сексуальным здоровьем и социальными связями, работу с зависимостями и поможет уменьшить возможную тревогу в связи с отменой антидепрессантов.

3. Description of research activities/Описание хода исследования

Participant in this study will clarify:

- His/her initial conditions through medical checkup
- Feeling initial questionnaires;
- Develop antidepressant discontinuation plan with psychologist;
- And lifestyle mentoring plan will be developed at the first 1,5 h online meeting depending on results of previous data.
- Lifestyle medicine program will consist of 18 months of every-week sessions 60 min duration via WhatsApp video and WhatsApp chat support between weekly sessions.
- Last 6 month is planned as follow-up, with WhatsApp chat support and online video consulting as it is needed for participant.
- During study and follow up, validated questionnaires will be used.

Будет выяснено:

- Изначальное состояние здоровья посредством медицинского чек апа
- Заполнены исходные опросники
- Разработан план отмены антидепрессантов совместно с психологом
- После получения всех данных, будет разработан индивидуальный план менторской программы по лайфстайл медицине во время первой 1,5 ч онлайн встречи
- Программа по лайфстайл медицине займет 18 мес и будет состоять из еженедельных 60 мин онлайн сессий посредством видеоконференций ватсапп и поддержкой в ватсапп чате между видео встречами
- Последние 6 мес планируется наблюдение, с поддержкой в ватсапп чате и онлайн видео консультациями по мере необходимости в зависимости от запроса участника
- Во время исследования и дальнейшего наблюдения будут использоваться валидированные опросники.

4. Risks/ discomfort involved/ Возможные риски/дискомфорт

There are possible potential risks, related to antidepressants discontinuation, might involve:

- Raising level of stress and anxiety
- Sleep problems, including insomnia and strange dreams
- Emotional discomfort
- Inability to concentrate
- Changing appetite
- Sexual health issues
- Fast or irregular heartbeat, low blood pressure or other physical symptoms, sometimes flu-like symptoms, problems with movement, such as problems with balance or walking, or involuntary movements
- Restlessness
- Changing in daily activities related to aspects mentioned above
- Sharing personal information or experiences during coaching might rise level of stress and anxiety

Nevertheless, all lifestyle interventions during this program are developed according to a participant needs and aimed to reduce all these possible negative symptoms, related with antidepressants discontinuation.

Существуют возможные риски, связанные с отменой антидепрессантов:

- Увеличение уровня тревоги и стресса
- Проблемы со сном, в том числе проблемы с засыпанием и странные сны
- Эмоциональный дискомфорт
- Невозможность сконцентрироваться
- Изменения аппетита
- Проблемы с сексуальным здоровьем
- Частые или неритмичные сердцебиения, пониженное артериальное давление или другие физические симптомы, такие как простудные, проблемы с движениями, такие как баланс при ходьбе или произвольные движения
- Беспокойство
- Изменение в повседневной активности вследствие описанных выше симптомов
- Обмен личной информацией или опытом во время коучинга может повысить уровень стресса и беспокойства.

Тем не менее, все вмешательства в образ жизни в рамках этой программы разрабатываются в соответствии с потребностями участников и направлены на уменьшение всех возможных негативных симптомов, связанных с прекращением приема антидепрессантов.

5. Expected impact/ Ожидаемый эффект

- Ability to stop antidepressant therapy with minimizing possible side effects and withdrawal effects due to its discontinuation

- Learning objectives about key moments of sleep hygiene, stress management and mental health, nutrition, physical activity
 - Improved health and well-being through working with sleep hygiene, stress management, indication proper physical activity level, proper nutrition, improving sexual health and social connections and working with addictions.
 - Developing skills and techniques to cope with anxiety and stress or other emotional episodes in future
 - Raising quality of life and non-communicable disease prevention
 - Access to personal consultations and support during the program and follow up period.
 - Developing program using lifestyle medicine for people who stop antidepressant therapy might have great scientific impact, considering that this kind of program is being held for the first time
-
- *Возможность прекращения терапии антидепрессантами с минимизацией возможных побочных эффектов и синдрома отмены.*
 - *Цели обучения по ключевым моментам гигиены сна, управления стрессом и психического здоровья, питания, физической активности.*
 - *Улучшение здоровья и благополучия посредством работы над гигиеной сна, управления стрессом, указания надлежащего уровня физической активности, правильного питания, улучшения сексуального здоровья и социальных связей, а также работы с зависимостями.*
 - *Развитие навыков и методов борьбы с тревогой, стрессом или другими эмоциональными эпизодами в будущем.*
 - *Повышение качества жизни и профилактика неинфекционных заболеваний*
 - *Доступ к личным консультациям и поддержке во время программы и последующего периода.*
 - *Разработка программы с использованием лайфстайл медицины для людей, прекративших терапию антидепрессантами, может иметь большое научное значение, учитывая, что такая программа проводится впервые.*
-
- 6. Dissemination of results/ Распространение результатов**
- Personal identifying information will be replaced with unique identifiers before data analysis to protect participants' identities.
 - Study results will be reported in an aggregate form, ensuring that individual participant data remains confidential.
 - Anyone involved in data analysis and dissemination will be required to sign confidentiality agreements to uphold the privacy of participants. Access to identifiable participant information will be restricted to designated individuals involved in data management and analysis, further safeguarding confidentiality.
 - Data will be stored securely on password-protected documents.
 - The study protocol, including plans for data dissemination and confidentiality measures, will undergo rigorous ethical review to ensure compliance with privacy regulations and guidelines.
 - *Личная идентификационная информация будет заменена уникальными идентификаторами перед анализом данных для защиты личности участников.*

- Результаты исследования будут сообщаться в совокупной форме, что гарантирует конфиденциальность данных отдельных участников.
- Все, кто участвует в анализе и распространении данных, должны будут подписать соглашения о конфиденциальности для обеспечения конфиденциальности участников. Доступ к идентифицируемой информации участников будет ограничен назначенными лицами, участвующими в управлении и анализе данных, что обеспечивает дополнительную защиту конфиденциальности.
- Данные будут надежно храниться в документах, защищенных паролем.
- Протокол исследования, включая планы распространения данных и меры конфиденциальности, пройдет строгую этическую проверку для обеспечения соответствия правилам и рекомендациям по конфиденциальности.

7. Further Information/ Дополнительная информация

Do not hesitate to ask questions regarding the aim of this study or the implementation of the study design. If you have any doubts or questions, do ask us for clarification.

Не стесняйтесь задавать вопросы относительно цели данного исследования или реализации плана исследования. Если у вас есть какие-либо сомнения или вопросы, обратитесь к нам за разъяснениями.

8. Freedom of consent/ Свобода согласия

You are a volunteer participant. You are free to withdraw your consent now or later.

Вы участник-волонтер. Вы можете отозвать свое согласие сейчас или позже.

Participant's declaration/ Декларация участника

I read this form and I understand the procedures involved. I agree to participate in this study.

Я прочитал эту форму и понимаю необходимые процедуры. Я согласен участвовать в этом исследовании.

Date/ Дата 22.12.2022

[Name and signature of
participant/ Имя и
фамилия участника]

Name and signature of
researcher/ Имя и
фамилия
исследователя]

[Name and signature of
witness/ Имя и подпись
свидетеля]

Appendix 3. Data extraction table

Table 4 Data extraction table

Authors, Type of study	Population, type of intervention	Mean age ± SD	Males (%)	Assessment	Main findings
Clinical trial Schmidt NB, Wollaway- Bickel K. et al, 2002 [146]	• N=22 patients with (PD); • CBT with AD discontinuation • CBT without AD discontinuation	40.6 ±10.0	41	PDSS, SPRAS, SDS, BDI	No significant group differences (between CBT+discontinuation and CBT + No Discontinuation)
RCT Huijbers MJ, Spinhoven P. et al., 2016 [148]	• N=249 patients with history of depressive episodes with full or partial remission. • MBCT+discontinuation (n=128); • MBCT+mADM (n=121)	NA	28; 37	SCID-I, IDS-C WHOQOL	The difference in relapse/recurrence rates exceeded the non-inferiority margin and time to relapse/recurrence was significantly shorter after discontinuation of mADM. There were only minor differences in depression severity.
Mixed- methods study combining quantitative and qualitative data, drawn from an RCT Huijbers M.J., Wentink C., et al., 2020 [149]	• N=226 recurrently depressed in partial or full remission. • MBCT followed by guided discontinuation of ADM or MBCT with continuation of ADM. • Full ADM discontinuation (n=82), • Partial ADM discontinuation (n=34) • No ADM discontinuation (n=110)	50±11.1, 52 ± 9.8; 51± 10.3	24; 47; 36	SCID	In MBCT with discontinuation 53% fully discontinued ADM within 6 months; 13% discontinued partially. Of the 82 patients who fully discontinued ADM within 6 months after baseline, 50% restarted ADM during the 15-months study period. Based on the SCID interviews, this might have been related to a relapse in 76% of them.

Authors, Type of study	Population, type of intervention	Mean age ± SD	Males (%)	Assessment	Main findings
Clinical trial Fava G.A., Grandi S., Zielezny M., et al., 1994 [64]	- N=40 patients with MDD with 3 or more episodes of depression, with the immediately preceding episode being no more than 2 with a minimum of 10-week remission. - CBT+tapering and AD discontinuation (n=20) - CM with tapering and AD discontinuation (n=20)	43.7 ± 2.3; 48.5 ± 3.3	40; 25	CID	Most of the residual symptoms were found to have occurred also in the prodromal phase of illness. CBT group has a significantly lower level of residual symptoms after drug discontinuation in comparison with CM group. 15% vs 35% at 2 years follow up (without statistical significance).
Clinical trial Fava G.A., Rafanelli C., Grandi S., Conti S., et al., 1998 [65]	- N=40 patients with MDD with 3 or more episodes of depression, with the immediately preceding episode being no more than 2 with a minimum 10-week remission. - CBT+pharmacotherapy (n=20) - CM+pharmacotherapy (n=20)	45.1±10.3; 48.7± 12.1	45; 35	CID	In CBT group - significant improvement in residual symptoms, no significant changes in the CM group. Comparison of residual symptoms at the second assessment (after CBT or CM) with their initial measurements as covariates, a significant effect of CBT was found, p<0,001. During the 2-year follow-up, 5 patients (25%) in the CBT group and 16 patients (80%) in the CM group relapsed.
Open preliminary study Psaros C., Freeman M., et al., 2014 [147]	- N=12 women with remitted MDD on maintenance ADs with a plan to discontinue ADs for pregnancy. - CBT-PR	34 ± 3.96	0	MINI, MADRS, QLESQ, CGI, 17-Item HRSD	Over the 24 weeks of the trial, 75% of participants did not restart ADs/did not relapse to depression. Of the 3 who reintroduced AD, 2 experienced a depressive relapse, whereas one did not meet full criteria for MDD.

Authors, Type of study	Population, type of intervention	Mean age ± SD	Males (%)	Assessment	Main findings
RCT Kuyken W., Byford S., et al., 2008 [150]	- N=123 patients with history of three or more previous episodes of depression, in full or partial remission from the most recent episode. - MBCT (n = 61) - mADM (n = 62)	48.95 ± 10.55; 49.37 ± 11.84	23; 24	SCID, 17-item HRSD, 21-item self- report BDI, WHOQOL- BREF	Relapse/recurrence rates over 15-month follow-ups in MBCT were 47%, compared with 60% in the mADM group. MBCT was more effective than mADM in reducing residual depressive symptoms and psychiatric comorbidity and in improving quality of life in the physical and psychological domains.
RCT Kuyken W., Hayes R., et al., 2015 [151]	- N=212 patients with three or more previous major depressive episodes and on a therapeutic dose of maintenance antidepressants. - MBCT-TS - mADM.	50± 12; 49± 13	29; 8	SCID, GRID-HAMD, BDI, MSCL, WHOQOL- BREF, EQ-5D-3L, HPQ	The time to relapse or recurrence of depression and the number of serious adverse events did not differ between MBCT-TS and mADM over 24 months p=0,43.
RCT Bockting C.L.H., Klein N.S., et al., 2018 [153]	- N=289 patients with previously experienced at least two depressive episodes in remission or recovery on antidepressants. - PCT+AD (n=104), - PCT+AD tapering (n=85), - AD alone (n=100)	47± 9.3; 47.7 ± 11.1; 47.2± 10.5	31; 38; 36	SCID-I, HRSD, IDS- SR, RRS, DAS, LEIDS and others	AD alone was not superior to PCT+tapering AD in terms of the risk of relapse or recurrence p=0,502. Adding PCT to AD resulted in a 41% relative risk reduction compared with AD alone p=0,026.

Authors, Type of study	Population, type of intervention	Mean age ± SD	Males (%)	Assessment	Main findings
RCT Segal Z.V., Bieling P., et al., 2010 [152]	160 aged 18 to 65 meeting DSM-IV for major depressive disorder with a minimum of 2 past episodes - mADM (n=28), - MBCT (n=26), - PLA+Clin (n=30)	45.8 ± 11.4; 44.8 ± 9.4; 41.9 ± 11.6	28,6; 50; 33,3	SCID, 17 item HRSD	Significant interaction between the quality of acute phase remission and subsequent prevention of relapse in randomized patients (p =0,03). Among unstable remitters (1 or more HRSD >7 during remission) patients in both MBCT and mADM showed a 73% decrease comparing to PLA+Clin (p =0,03). For stable remitters (all HRSD ≤ 7 during remission) no group differences in survival.
Case series Whittal M.L., Otto M.W., et al., 2001 [66]	8 patients with PD who discontinued SSRI, structured group program of CBT.	20, 36, 43, 44, 31, 29, 31, 32	12,5	ADIS interview, ASI, MI, FQ, BAI, BDI,	All patients successfully discontinued their SSRI medication while demonstrating clinical improvement. These results were maintained at 3-months follow-up.
Case report Brogan K., Jarvi A., Anderson S., Kalen Flynn S., 2020 [100]	1 woman with history of major depressive disorder, multiple suicide attempts, extensive trauma and abuse, and substance abuse presented for outpatient management. - Intervention: diet, hydration, yoga, exercise, meditation	50	0	Symptoms evaluation	This case is evidence of the role of lifestyle interventions in treating protracted withdrawal symptoms associated with discontinuing psychotropic medications.

Authors, Type of study	Population, type of intervention	Mean age ± SD	Males (%)	Assessment	Main findings
Case report Brogan K., Siefert A., 2019 [101]	1 woman history of GAD, MDD, AN, and PTSD - Intervention: diet, yoga, exercise, meditation, psychological support, cranial electrical stimulation, EFTs, acupuncture	38	0	Symptoms evaluation	The patient experienced remarkable symptom remission after strategic discontinuation of medications through the addition of the lifestyle interventions. She was also able to heal the root-cause drivers of her psychiatric diagnoses. Currently she is symptom-free and medication-free after nearly 21 years.
Clinical trial Kuyken W., Dalglish T., Watkins E., Holden E., White K., et al., 2010 [67]	123 patients with recurrent depression. Treatment adherence (TA gr): - MBCT+discontinuation (n=114) - mADM (n=52) After treatment additional evaluation for cognitive reactivity (CR gr) - MBCT+discontinuation (n=43) - mADM (n=37)	TA gr: 50±10.64; 49 ±11.84 CR gr: 48.35 ±10.68; 49.27 ±11.53	TA gr : 21; 24 CA gr: 16; 22	HRSD, KIMS, SCS, DAS, pre-/post-mood induction visual analogue scale (for sad music listening)	MBCT was associated with significantly greater improvement on both the SCS and KIMS relative to mADM. According to examination, whether either SCS change or KIMS change moderated the significant main effect relationship in the cognitive reactivity sub-sample (n = 80) between reactivity and outcome, using the same regression approach. There were no significant effects involving the KIMS, $p > 0.5$. For the SCS however, there was a significant interaction between SCS change and cognitive reactivity in the prediction of HRSD-15m scores indicative of moderation.

Appendix 4. HADS (Hospital anxiety and depression scale)

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			I feel as if I am slowed down:
3		Most of the time	3		Nearly all the time
2		A lot of the time	2		Very often
1		From time to time, occasionally	1		Sometimes
0		Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			I get a sort of frightened feeling like 'butterflies' in the stomach:
0		Definitely as much	0		Not at all
1		Not quite so much	1		Occasionally
2		Only a little	2		Quite Often
3		Hardly at all	3		Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			I have lost interest in my appearance:
3		Very definitely and quite badly	3		Definitely
2		Yes, but not too badly	2		I don't take as much care as I should
1		A little, but it doesn't worry me	1		I may not take quite as much care
0		Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			I feel restless as I have to be on the move:
0		As much as I always could	3		Very much indeed
1		Not quite so much now	2		Quite a lot
2		Definitely not so much now	1		Not very much
3		Not at all	0		Not at all
		Worrying thoughts go through my mind:			I look forward with enjoyment to things:
3		A great deal of the time	0		As much as I ever did
2		A lot of the time	1		Rather less than I used to
1		From time to time, but not too often	2		Definitely less than I used to
0		Only occasionally	3		Hardly at all
		I feel cheerful:			I get sudden feelings of panic:
3		Not at all	3		Very often indeed
2		Not often	2		Quite often
1		Sometimes	1		Not very often
0		Most of the time	0		Not at all
		I can sit at ease and feel relaxed:			I can enjoy a good book or radio or TV program:
0		Definitely	0		Often
1		Usually	1		Sometimes
2		Not Often	2		Not often
3		Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

Appendix 5. SATED Questionary (Satisfaction, Alternes, Timing, Efficiency, Duration)

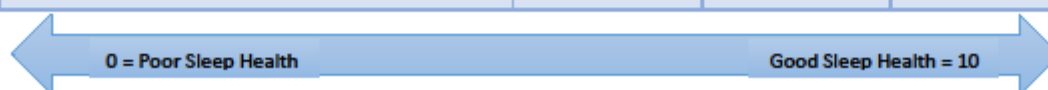
Chronophysiology & Sleep Hygiene Training

GOOD SLEEP HYGIENE

DO:	
1. Go to bed and get up at the same time. Try to maintain something close to this on weekends.	
2. Get regular exercise each day, preferably in the morning (evidence that exercise (including stretching/aerobic) improves restful sleep.	
3. Get regular exposure to outdoor or bright light, especially in the afternoon.	
4. Keep temperature in your bedroom comfortable.	
5. Keep bedroom quiet and dark enough to facilitate sleep	
6. Use your bed only for sleep (and sexual activity).	
7. Establish a regular, relaxing bedtime routine. (ex: warm bath/shower, aromatherapy, reading, music).	
8. Use a relaxation exercise before going to sleep or relaxing imagery.	
9. Keep your feet and hands warm. Wear warm socks to bed.	
10. Designate another time to write down problems and possible solutions (ex: late afternoon/early evening).	
DONT:	
1. Exercise before going to bed.	8. Take daytime naps (No longer than 20 minutes).
2. Engage in stimulating activities just before bed.	9. Command yourself to go to sleep.
3. Have caffeine in the evening (coffee, teas, etc.)	10. Watch the clock or count minutes.
4. Read or watch television in bed.	11. Lie in bed awake more than 20-30 minutes.
5. Use alcohol to help you sleep.	12. Succumb to maladaptive thoughts.
6. Go to bed to hungry or to full.	13. Change your daytime routine the next day if you didn't Sleep well.
7. Take another person's sleeping pills.	14. Increase caffeine intakes the next day.

SATED QUESTIONNAIRE

	Rarely/Never (0)	Sometimes (1)	Usually/Always (2)
1. Are you satisfied with your sleep?			
2. Do you stay awake all day without dozing?			
3. Are you asleep (or trying to sleep) between 2:00 am and 4 am?			
4. Do you spend less than 30 minutes awake at night? (This includes the time it takes to fall asleep and awakenings from sleep.)			
5. Do you sleep between 6 and 8 hours per day?			



Ref: Mastin, Bryson, Corwyn. Assessment of Sleep Hygiene Using the Step Hygiene Index. *Journal of Behavioral Medicine*. 20016

Appendix 6. EQ-5D-3L (European Quality of Life 5 Dimensions 3 Level Version)

Figure 1/UK (English) EQ-5D-3L Paper Self-Complete (sample version)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

SELF-CARE

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

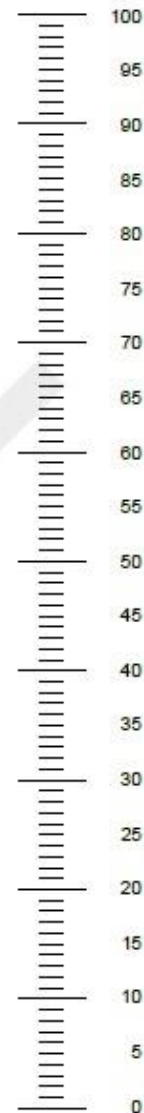
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

7

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

The best health
you can imagine

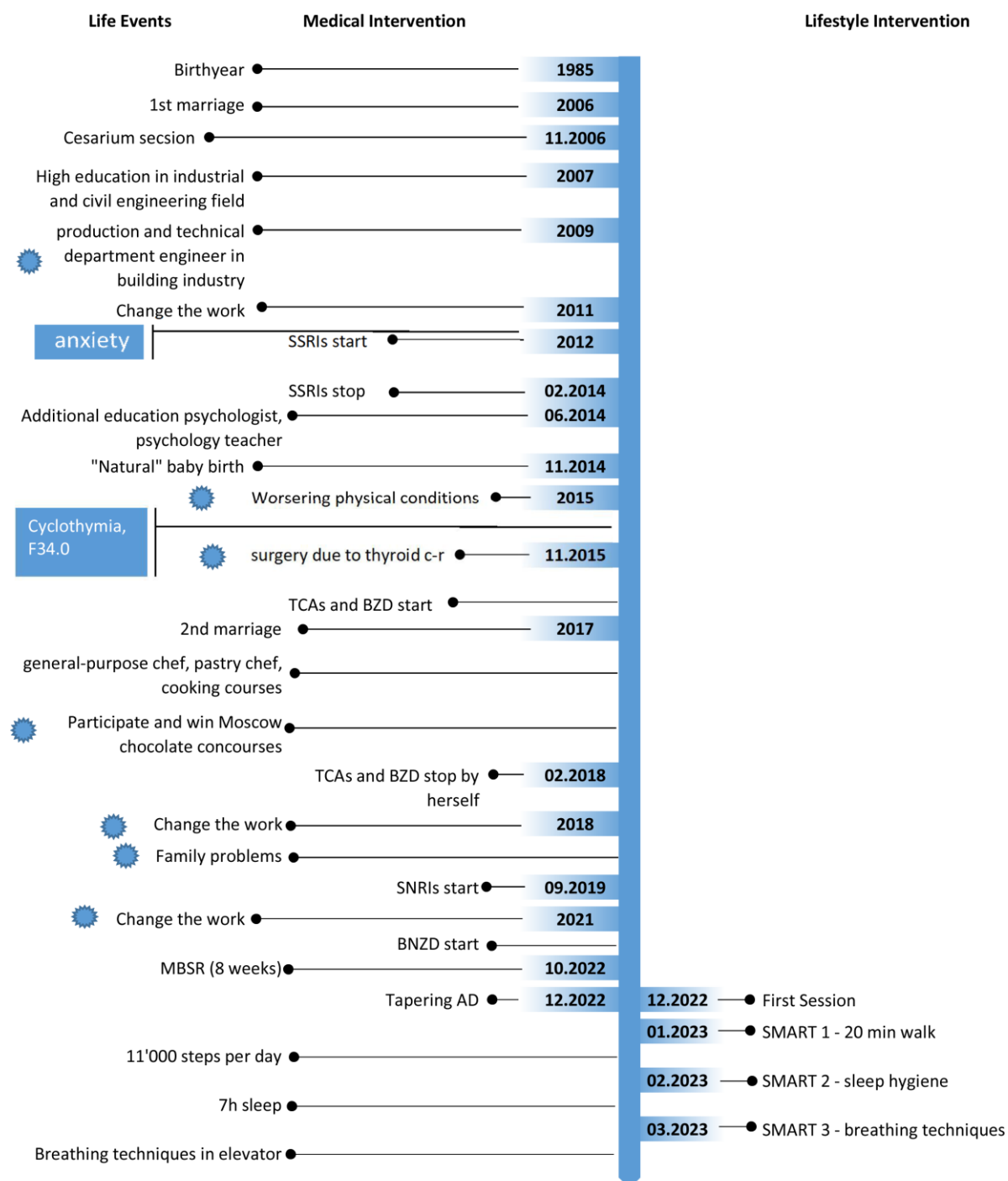


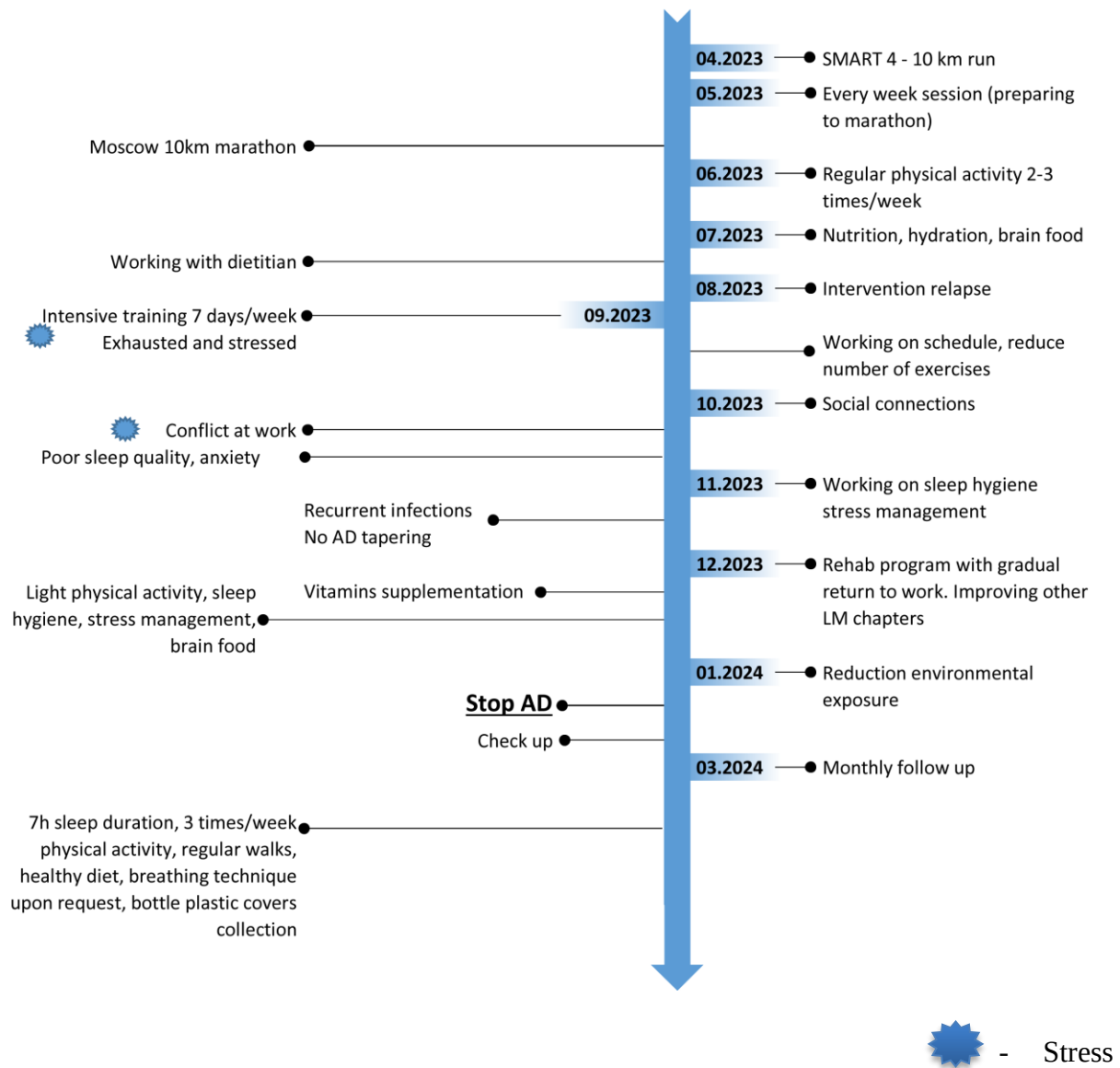
The worst health
you can imagine

In previous versions of the EQ-5D-3L, the numerical scale straddled the EQ VAS (provided in the annex for reference). Users are encouraged to use the latest version of the EQ-5D-3L in new studies.

Appendix 7. Timeline

Figure 8 Timeline





Appendix 8. Bioimpedance results

Table 5 Bioimpedance results

Date	Weight	BMI	WTH	Fat mass (kg)	Fat mass (%)	Muscular mass (kg)	Muscular mass (%)	Extracellular fluid (kg)	Intracellular fluid (kg)	Ccal	Ccal/m ²
Normal		18,5-25	0,71-0,85	10,2-17,0	20-30	18,2-24,3	43,5 - 48,0	12,1 - 16,0	16,8 - 20,8		777,0 - 900,0
12.2018	65	22,5	0,80	23,0	35,4	19,1	45,5	12,9	-	-	808,2
11.2021	66	23,0	0,85	23,6	35,7	19,1	45,1	13,0	18,1	1436	818,2
11.2023	64,5	22,3	0,79	19,6	30,4	21,1	46,9	13,6	19,2	1490	854,0
12.2023	64,5	22,3	0,83	20,8	32,2	20,1	46,0	13,1	18,9	1499	858,9
01.2024	63,8	22,1	0,79	19,5	30,5	20,7	46,7	13,4	19,0	1489	856,8
03.2024	61,5	21,3	0,79	18,5	30,0	19,9	46,3	13,0	18,5	1451	846,3
04.2024	60	20,8	0,91	14,9	24,8	21,7	48,1	13,6	19,4	1504	884,5
05.2024	60	20,8	0,75	13,5	22,5	22,7	48,9	14,0	20,0	1527	898,5

Appendix 9: Copyright Statement

Affirmation

The undersigned Elizaveta Kuznetsova postgraduate student of the Postgraduate Program "LIFESTYLE MEDICINE" of the University of Thessaly

I declare responsibly that I accept the following terms concerning:

(a) the copyright of my Master's Thesis entitled "Lifestyle medicine vs withdrawal of antidepressants 'effect'"

(b) the management of the research data I will collect in the course of its elaboration:

1. The copyright of the resulting volume of the master's thesis will belong to me. I will follow the instructions for writing, printing and depositing copies of the dissertation in the relevant repositories (in printed and/or electronic form).
2. The management of the dissertation data belongs jointly to me and the Director of Studies/Main Supervisor.
3. Any scientific publication or announcement (posted or oral), or reference derived from the material/data of this work will be made with authors myself, the main supervisor and/or other researchers (such as a member of the three-member advisory committee), depending on their contribution to the research or the writing of the research paper(s).
4. The order of names in scientific publications or scientific announcements will be decided jointly by me and the main supervisor (DOS) of the project before it begins. This decision will be certified in writing between myself and the main supervisor.

Finally, I declare that I am aware of the rules on plagiarism and intellectual property and that I will strictly follow them throughout my studies, I will attend to the educational obligations arising from this MSc, as well as will attend the publication procedures that will arise after the completion of my studies.

17.06.2024

Elizaveta Kuznetsova