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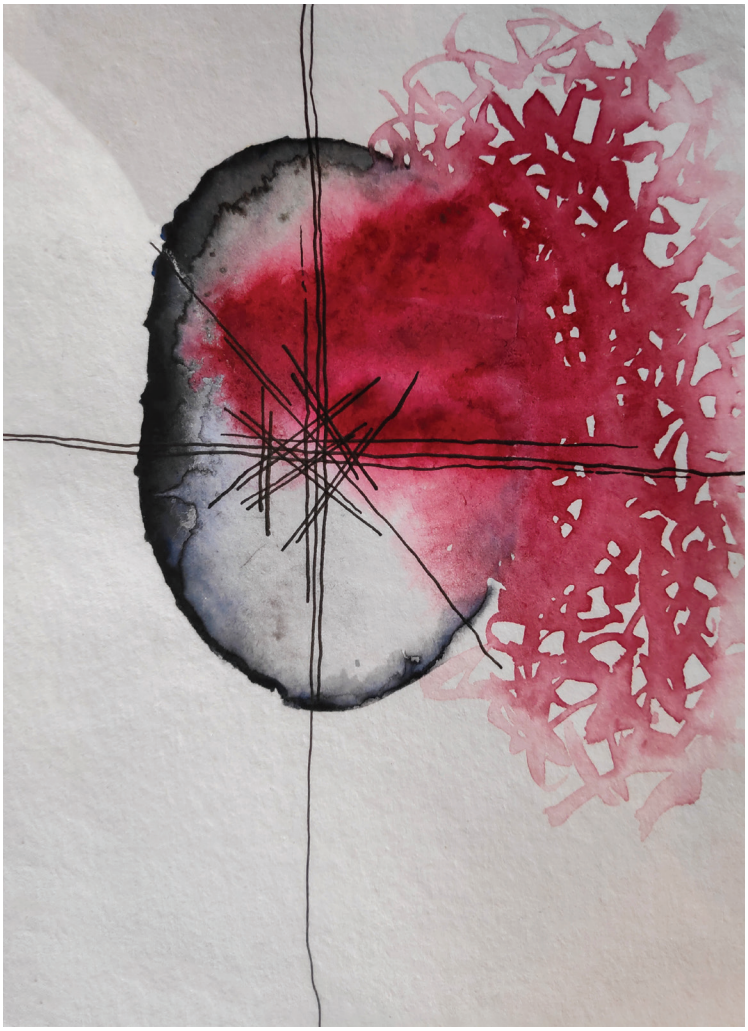

Lietuvos sveikatos mokslų universiteto (LSMU) Neuromokslų institutas,
Lietuvos biologinės psichiatrijos draugijos (LBPD) organizuojamos mokslinės-praktinės konferencijos (nuotolinė)

“Šiandienos psichofarmakoterapijos aktualijos: kalba klinikiniai praktikai“

2020 m gruodžio mėn. 17 d.

Programa

14.00 val. Konferencijos atidarymas LBPD prezidentė *prof. dr. Vesta Steiblienė* ir LBPD viceprezidentas *gyd. Edgaras Diržius*

I dalis. Psichozinių sutrikimų psichofarmakoterapija

14.05 val. Kada jau laikas ilgo veikimo antipsichoziniam vaistui. *Prof. dr. Vesta Steiblienė*

14.35 val. Gydymas pailginto veikimo Aripiprazolu – kaip pasikeitė paciento gyvenimas? *Gyd. Ieva Šveikauskienė*

14.55 val. Šizofrenijos simptomų kontrolė su Paliperidono palmitatu. *Gyd. Stefa Naujokienė*

15.15 val. Kariprazinas – ar tikrai tik negatyviems simptomams? *Gyd. Algirdas Dambrava*

15.35 val. Klausimai ir diskusija su lektoriais.

II dalis. Afektinių sutrikimų psichofarmakoterapija

16.00 val. Rezistentiškos gydymui depresijos diagnostika ir gydymo praktiniai aspektai. *Dr. Edgaras Dlugauskas.*

16.20 val. SSRI ar Vortioxetinas – kokie prioritetai: gydytojo praktiko įžvalgos. *Dr. Devika Gudienė*

16.40 val. Antidepresantų nepageidaujami poveikiai: stebėsena ir valdymas klinikinėje praktikoje. *Prof. dr. Vesta Steiblienė*

17.00 val. Nėštumas ir maitiniamas krūtimi: saugumas skiriant psichotropinius vaistus. *Gyd. R. Mazaliauskienė*

17.20 val. Generalizuoto nerimo sutrikimo psichofarmakoterapijos galimybės. *Prof. dr. V.Steiblienė*

17.35 val. Klausimai ir baigiamoji diskusija su lektoriais. Konferencijos uždarymas.

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TURINYS

Dear colleagues,

We are living in unprecedented times. The Coronavirus pandemic is causing an enormous burden for the Global economy and health. As noted by the Director-General of the World Health Organization, Tedros Adhanom Ghebreyesus "The pandemic is a once-in-a-century health crisis, the effects of which will be felt for decades to come". The unpredictability of this situation might bring up various experiences of uncertainty and danger. Research studies have already confirmed the huge negative influence of the pandemic on our mental health.

However, as scientists and clinicians, we might help others to shift their perspective towards healthy coping with the situation. Instead of ruminating on possible harms of the pandemic we might learn new skills and methods to deal with the difficult situations in our lives. It might be through exercising, meditating, problem solving, balancing your day, healthy eating or limiting exposure to media and the Internet.

The paraphrase of the very well-known holiday season song "Baby it's COVID outside" suits our times well, as we have not been so physically distant with each other in a long time. Yet, one of the most important feelings that should be attributed to healthy coping is the idea that we are all together in this. Let's support each other in these difficult times. Ask each other about coping strategies, feelings and whether help is needed in any way. We will get through this, we will learn and we will be stronger than ever, to face any new challenges the future might bring. Let's stay physically distant but with our hearts closer than ever.

It is my great pleasure to welcome you to the last issue of 2020.

In our first article Liaugaudaite et al. examine gender differences in psychosocial factors among suicide completers. They found that the most prevalent factors associated with suicide among men were interpersonal stressors, family conflicts, problems at work and financial difficulties, while amongst women the most prevalent factors were health problems, and bereavement.

Stanyte and Smigelskas investigate the effect of elicited emotional states on women's reaction to food cues. Their results indicate that negative and positive emotional states do not affect women's reaction to food cues or attention bias to food stimuli as measured through a visual dot-probe task.

Zeleckyte, Briliute and Steibliene review associations between womens loss of reproduction capacity and depressive disorder. The authors suggest that infertility can affect women's social, physical and psychological well-being and lead to social isolation. Patients with infertility often complain of stress and affective disorders, of which anxiety and depressive disorders (because of the infertility or infertility treatment) are the most common.

Laurinaitiene, Laurinaitis and Steibliene review the role of testosterone in clinical manifestation of mental disorders and type 2 diabetes. The findings of this study suggest that testosterone augmentation may be a potential therapeutic strategy in patients with anxiety, depression, neurodegenerative disorders or type 2 diabetes.

Due to high number of requests, we also translated an international consensus statement on monitoring for antidepressant-associated adverse events in the treatment of patients with major depressive disorder written by Dodd et al. into Lithuanian. The statement summarizes that adverse outcomes risks of antidepressant treatment can be managed through appropriate assessment and monitoring to improve the risk benefit ratio and clinical outcomes.

Pranckeviciene and Salciunaite provide a book review "Learning to deal with Problematic Usage of the Internet". The authors suggest this work might be of the utmost importance in helping to manage healthy Internet usage during the pandemic.

Finally, we introduce Lygnugaryte-Griksiene's dissertation thesis exploring skills for suicide intervention by emergency medical care doctors and nurses. The author discusses various factors contributing to skills for suicide intervention development, including sociodemographic factors, attitudes and burnout syndrome.

Yours sincerely,

Julius Burkauskas

Editorial Board Member of Biological Psychiatry and Psychopharmacology

Psychosocial Autopsy Study of Suicide in Lithuania: Gender Differences

Savižudybių psichosocialinės autopsijos tyrimas Lietuvoje: lyčių skirtumai

Vilma LIAUGAUDAITE[1], Nida ZEMAITIENE[2], Nijole RASKAUSKIENE[1], Laura DIGRYTE-SERTVYTIENE[2], Irina BANIENE[2], Valija SAP[2], Alicja JUSKIENE[1]

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SUMMARY

Background. Psychosocial autopsy is one of the most valuable methods to examine the relationship between antecedents and suicide. This method involves collection of data from relatives/acquaintances/friends or people who known well the suicide completers. This can help reconstruct the psychosocial environment of suicide completers and understand the circumstances of their death.

Aim. This study aimed to examine gender differences in psychosocial factors among suicide completers.

Methods. Subjects of this study included 145 suicide completers whose closest relatives/acquaintances/friends or people who know them well consented to participate in this study. Gender differences on psychosocial factors of suicide completers were analyzed by using information collected for the psychosocial autopsy study. Descriptive analyzes was performed to analyze age, gender, suicide method, place where the suicide occurred, the suicide completers socioeconomic profile, and risk factors of suicide completers.

Results. Of the 145 suicide completers, 111 (76.5%) were male and 34 (23.5%) were female (ratio 3:1) and 38% have had a history of previous non-fatal suicide attempt. Overall, among suicide completers most men (30%) and women (26%) were young adults aged 18 to 30 years, followed by middle-aged men (21%) and women aged 70+ (26%). The most prevalent factors associated with suicide among men were linked to interpersonal difficulties, family difficulties, difficulties in work and financial problems; while among women the most prevalent factors were health problems, and bereavement. Among all suicide completers, women had a significantly higher prevalence of past suicide attempts than men (58.8% vs. 32.4% respectively, p=0.022). Mental disorders were reported more frequently in women than men (56% vs. 34%, p=0.027). Of these, 56% of men and 73% of women regularly visited family doctors and other health specialists. History of mental disorders was reported in 29% of suicide completers: 23% of men, 47% of women.

Conclusions. Most of suicide completers were young adults, of both genders, aged 18 to 30 years, followed by middle-aged men and women aged 70+. The most prevalent factors associated with suicide among men were interpersonal stressors, family conflicts, problems in work and financial difficulties, while among women the most prevalent factors were health problems, and bereavement. A higher proportion of men suffered from drug and alcohol abuse.

Keywords: suicide, gender differences, psychosocial autopsy.

SANTRAUKA

Įvadas. Psichosocialinės autopsijos tyrimas grindžiamas duomenų rinkimu iš artimųjų/pažįstamų/draugų ar asmenų, gerai pažinojusių nusižudžiusius asmenis. Šie duomenys gali padėti atkurti nusižudžiusių asmenų psichosocialinę aplinką ir tokiu būdu suprasti savižudybių aplinkybes.

Tikslas. Ištirti nusižudžiusių asmenų psichosocialinių veiksnių skirtumus tarp lyčių, naudojant psichosocialinės autopsijos metodą.

Metodai. Tyrimo imtį sudarė 145 nusižudę asmenys, kurių artimiausi giminaičiai/pažįstami/draugai, gerai pažinoję nusižudžiusįjį, sutiko dalyvauti tyrime. Psichosocialinės autopsijos pagalba buvo išanalizuoti nusižudžiusių asmenų psichosocialiniai veiksniai ir jų skirtumai tarp lyčių. Aprašomoji duomenų analizė buvo atlikta siekiant apibūdinti tiriamąją imtį pagal amžiaus grupes ir lytį, savižudybės metodą, savižudybės vietą, nusižudžiusių asmenų socialinį ir ekonominį profilį bei rizikos veiksnius.

Rezultatai. Iš 145 nusižudžiusių asmenų 111 (76,5 proc.) buvo vyrai ir 34 (23,5 proc.) moterys (santykis 3:1). Ankstesnių savižudiškų bandymų turėjo 38 proc. Dauguma musižudžiusių vyrų (30 proc.) ir moterų (26 proc.) buvo jauno amžiaus, nuo 18 iki 30 metų; šiek tiek mažiau buvo vidutinio amžiaus vyrų (21 proc.) ir vyresnių nei 70 metų moterų (26 proc.). Interviu metu, nusižudžiusių asmenų artimųjų dažniausiai nurodomos savižudybės aplinkybės (mažėjančia tvarka) tarp vyrų buvo susijusios su tarpasmeniniais sunkumais, sunkumais šeimoje, darbo ir finansinėmis problemomis; o tarp moterų – su sveikatos problemomis ir netektimis. Ankstesnių bandymų žudytis dažnis tarp moterų buvo didesnis nei vyrų (atitinkamai 58,8 proc. ir 32,4 proc., p = 0,022). Moterų, lyginant su vyrais, psichikos sutrikimai buvo stebėti dažniau (atitinkamai 56 proc. ir 34 proc., p = 0,027). Iš jų 56 proc. vyrų ir 73 proc. moterų reguliariai lankėsi pas šeimos gydytoją ir kitą specialistą. Psichikos sutrikimų, kuriuos paminėjo nusižudžiusiųjų artimieji, galėjo turėti 29 proc. nusižudžiusių asmenų: 23 proc. vyrų, 47 proc. moterų.

Išvados. Daugiausia mirusiųjų dėl savižudybės, abiejų lyčių, buvo 18–30 metų amžiaus, vyrų – vidutinio amžiaus, ir moterų nuo 70 metų amžiaus. Vyrai, dažniau negu moterys, prieš savižudybę patyrė tarpasmeninius stresorius, konfliktus šeimoje, turėjo problemų darbe ir finansinių sunkumų. Tuo tarpu moterys, dažniau negu vyrai, turėjo sveikatos problemų ir netekčių. Didesnė dalis vyrų nukentėjo nuo piktnaudžiavimo narkotikais ir alkoholiu.

Raktažodžiai. savižudybė, lyčių skirtumai, psichosocialinė autopsija.

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INTRODUCTION

Although the suicide rate in Lithuania is on a consistent decline, the overall number of people taking their own lives remains rather high, that which highlights problems in the mental health system [1, 2]. Lithuania ranks fourth in the world's suicide rate, and has a second rank for the male suicide rate among all countries in the world [3]. The most vulnerable groups include mid-aged (45–59 years) and over 75 years old males living in rural and socially isolated environment [4]. Available information on risk for suicide completion in women is limited. Despite a high suicide rate among these groups, there is a significant lack of empirical evidence on their suicide behavior [5]. To improve prevention and detection of suicide risk factors, more research is needed on gender differences in contributors to suicidal behavior and associations between precipitating factors and suicide means [6]. Psychosocial autopsy study is probably the most direct technique currently available for determining the relationship between particular antecedents and suicide [7, 8]. This can help reconstruct the psychosocial environment of suicide completers and thus understand the circumstances of their death.

We examined the characteristics of suicide completers aged 18 years and older using data from the semi-structured interview of relatives/acquaintances/friends or people who know well the suicide completers and who agreed to participate in this study. The study took into account data by age range and gender, suicide method, place where the suicide occurred, socioeconomic profile, and the circumstances related to most common difficulties experienced by suicide completers.

MATERIAL AND METHODS

Subjects

Subjects of this study included 145 suicide completers whose closest relatives/acquaintances/friends or people who know well consented to participation in our study. The investigator chose bereaved (informant) who replied, and could participate in an interview.

Procedures

A present study with 145 suicide cases/informants was undertaken from January 2017 to December 2019. The study data was collected using a semi-structured interview method that was based on a protocol specifically designed for this study. A semistructured interview was conducted with adult (older than 18 years old) relatives/acquaintances/friends or people who know well the suicide completers and the suicide was at least six months ago, but no more than three years ago. The participants of study were invited through media, social media, universities, health institutions, crisis centers, and mental health centers. More people responded to the invitation of this study after published psychoeducational articles and shared invitations from famous people in social media and less from the communication with the administration of municipal or institutions offering a psychosocial help. The study participants were Lithuanian citizens, from various areas of Lithuania. The participants were informed about the study and were able to withdraw from the study at any time of the study. The confidentiality of information supplied by the research participants was guaranteed. Participation in the study was voluntary, and the research participants provided written consent thereof. The study protocol was approved by the Kaunas Regional Biomedical Research Ethics Committee.

Assessment measures

This study was conducted based on the psychosocial suicide autopsy interview method. A semi-structured interview was administered by psychologists. The interview consisted of 57 open and closed questions covering the following main groups of questions: a) socio-demographic data about the people who committed suicide and their relatives; b) short prehistory of suicide and circumstances related to most common difficulties experienced by suicide completers (e.g. family conflicts, interpersonal relationships, bereavement, abuse, financial and health problems, problems in work and study, and others); c) physical and mental health, the use of medical services. The interviews were taken place at either private rooms of district municipalities, crisis centers, or community mental health centers. Confidentiality was guaranteed. The duration of the interview was, in average, 1.5 hours.

Statistical analysis

All statistical analyses were executed using the Statistical Package for Social Sciences (SPSS) for Windows (version 17.0). We analyzed gender differences in psychosocial and psychiatric characteristics of suicide completers using information collected for the study. Variables included for data analysis were sociodemographic, suicide related characteristics, previous suicidal behaviors and family history of suicidal behaviors, and medical problems. Pearson's Chi Square test, and Fisher's exact test were used to examine frequencies, T-test analysis was used to determine the significance of the difference between mean values in the independent groups. Because of the small numbers and the incompleteness of data available for many variables, statistical analysis for this report is mainly limited to counts and percentages. All findings are indicative, and no significance testing of differences was carried out. Due to the smaller number of women who died by suicide, breakdowns by gender may not always be provided. Statistical significance was accepted at $p<0.05$.

RESULTS

Among analyzed of the 145 suicide completers, 111 (76.5%) were men and 34 (23.5%) were women. The mean age was 41±17 (range 18–85) years in the male group, 49±22 (range 18–87) years in the female group (total 43±18, range 18–87) (Table 1).

More than a third (38%) of the all suicide completers were aged 31 to 50 years old. The higher differences in age group between males and females were in the 31–40 age group (19% vs. 9%) and 70+ age group (8% vs. 26%).

Sociodemographic characteristics of suicide completers

In our study sample, more than a half (59%) of suicide completers lived in the urban and 39% in rural area; only 2% (3 suicides completers) lived outside of Lithuania. The majority of suicide completer (40%) were married, 34.5% never married, 17.9% divorced or separated, and 7.6% were widowed. According to gender, more than half (65%) of women were never married or widowed. Among all suicide completers of our study, around a quarter (22%) had higher university education. A half (52%) of study sample were employed, while 18% were unemployed, 12% were students, 16% were retired and 4% unable to work due to illness or disability.

Table 1. **Sociodemographic characteristics of suicide completers**

Characteristics	All, N=145	Men, N=111	Women, N=34	p men vs. women
Age, mean (SD) min–max	43 (18)18–87	41 (17)18–85	49 (22)18–87	p=0.039
Age group, n (%)				χ^2=10.7 p=0.058
18–30	42 (29.0)	33 (29.7)	9 (26.5)	
31–40	24 (16.6)	21(18.9)	3 (8.8)	
41–50	31 (21.4)	25 (22.5)	6 (17.6)	
51–60	19 (13.1)	16 (14.4)	3 (8.8)	
61–70	11 (7.6)	7 (6.3)	4 (11.8)	
70+	18 (12.4)	9 (8.1)	9 (26.5)	
Region, n (%)				χ^2=1.9 p=0.585
rural	57 (39.4)	44 (39.6)	13 (38.2)	
urban	85 (58.6)	64 (57.7)	21 (61.8)	
other	3 (2.1)	3 (2.7)	0	
Marital status, n (%)				χ^2=39.0 p<0.001
married	58 (40)	50 (45.1)	8 (23.4)	
mever married	50 (34.5)	39 (35.1)	11 (32.4)	
divorced/separated	26 (17.9)	22 (19.8)	4 (11.8)	
didowed	11 (7.6)	0	11 (32.4)	
Education, n (%)				χ^2=4.1 p=0.668
primary	7 (4.8)	5 (4.5)	2 (5.9)	
lower secondary	19 (13.1)	14 (12.6)	5 (14.7)	
upper secondary	30 (20.7)	22 (19.8)	8 (23.5)	
vocational education and training	40 (27.6)	34 (30.6)	6 (17.6)	
post-secondary	16 (11.0)	10 (9.0)	6 (17.6)	
university	32 (22.1)	25 (22.5)	7 (20.6)	
unknown	1 (0.7)	1 (0.9)	0	

Suicide methods and place

Among all suicide completers, 38% have had a history of previous non-fatal suicide attempt. A higher proportion of females experienced a history of suicide attempts compared with males (58.8% vs. 32.4%, p=0.022).

Around three-quarters (73.1%) of the all of 145 suicides were completed by hanging, strangulation or suffocation (Table 2). For both male and female subjects, hanging was the most frequently used suicide method (74.8% and 67.7% respectively). The second most common method of suicide was jumping from a height (7.5 %). The suicide rate by jumping from a height and by poisoning among female suicide completers is greater than among men. In contrast, eight (7.2 %) of male subjects used a firearm.

Other methods' accounted for 9.6% of all suicides, comprising of methods, such as drowning (3 women), suicides on the railway (4 men), used a sharp tool (1 man), suicides via poisoning by alcohol and/or recreational drugs (1 man and 1 woman), by opening veins (2 men), carbon monoxide poisoning (1 man), electrocute in the bath (1 man).

Overall, men were more likely to use firearms, suicides on railway and more likely to use hanging than women, while women were more likely to use jumping from a height, poisoning and drowning as suicide method.

Most suicides took place at the individual's home (56%, n=81) or nearby workshop, outbuilding, basement or garage (14%, n=21). The next most common location was parents', grandparents' homes, or near them (11%, n=16), woodland or park (8%, n=12), followed by railway (2%, n=4).

Difficulties perceived by suicide completer prior suicide

The circumstances related to interpersonal relationships, health problems, and bereavement most commonly were reported by interviewing relatives/friends of suicide completers (Figure 1).

Overall difficulties experienced by suicide completers and generally restricted to the previous 12 months (yes vs. no/

Table 2. **Suicide methods by gender**

	Suicide method, N (%)				
	Hanging/ suffocation	Jumping from a height	Poisoning	Firearm	Other methods
All (N=145)	106 (73.1)	11 (7.5)	6 (4.1)	8 (5.5)	14 (9.6)
Men (N=111)	83 (74.8)	6 (5.4)	4 (3.6)	8 (7.2)	10 (9.0)
Women (N=34)	23 (67.6)	5 (14.7)	2 (5.9)	–	4 (11.7)

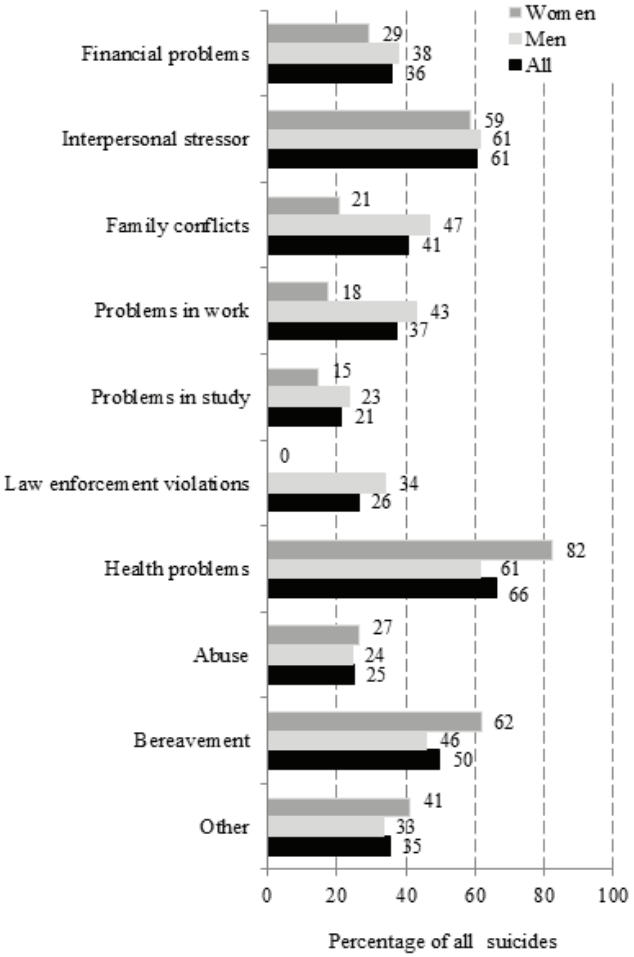


Figure 1. **Difficulties experienced by suicide completers by gender**

unknown), reported by interviewing relatives/friends of suicide completers, were related to: health problems (66%, n=96), interpersonal stressors (61%, n=88), family conflicts (41%, n=59), financial problems (36%, n=52), bereavement (50%, n=72). Over a quarter (26%, n=38) of suicide completers were known to have been involved with the criminal justice system (this includes a history of prison, or other remand).

According to the data, there was evidence of either history or current emotional, sexual, physical, financial or other type of abuse in 25% (n=36) of suicide completers. The largest proportions were for physical and emotional types of abuse: aggressive father or stepfather in childhood (10%, n=15), parents did not show love in their teens (n=1), male violence against women (4%, n=6), battles on the street (6%, n=9). Some people experienced more than one type of abuse. More than a half (56%) of suicide completers suffered four or more difficulties.

Table 3. **History of physical health conditions in suicide completers**

Disease	N (%)
Cardiovascular system disorders	8 (5.5)
Metabolism or nutritional disorders	8 (5.5)
Musculoskeletal disorder	6 (4.1)
Cancer (prostate, breast, cervical, brain tumor)	6 (4.1)
Digestive system disorders	4 (2.8)
Retarded development	4 (2.8)
Traumas	3 (2.1)
Respiratory system disorders	2 (1.4)
Infectious diseases	2 (1.4)
Post stroke	2 (1.4)
Epilepsy	2 (1.4)
Eye (glaucoma)	1 (0.7)
General or unspecified health problems (Asperger syndrome, hay fever, hepatitis)	11 (7.6)

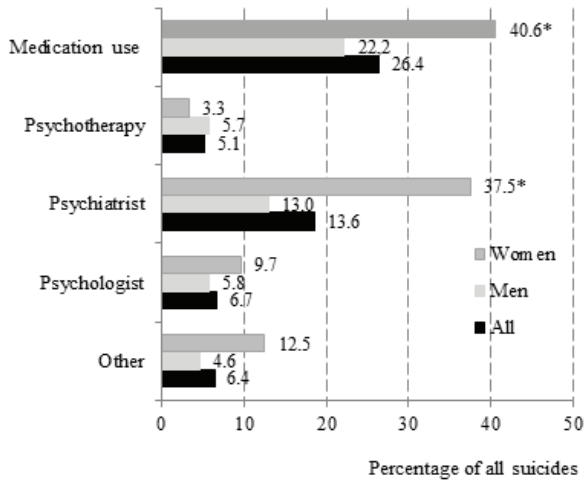
Differences in experienced difficulties between suicide completers by gender are presented in Figure 1. They are most pronounced for health problems (61% of men vs. 82% of women), bereavement (46% vs. 62%), family conflicts (47% vs. 21%), financial problems (38% vs. 29%) and involvement with the criminal justice system (only 34% of men).

Over a quarter (28%, n=41) of suicide completers had a family history of suicide, with similar proportions for men (28%, n=31) and women (29%, n=10).

History of health disorders and use of mental health services

According to the data collected history of implied (no diagnosed) physical illness was reported in 39% (n=57) of suicide completers, significantly more frequently in women than men (56%, n=38 vs. 34%, n=19 suicides; p=0.027). As reported, of these, 56% (n=20) of men and 73% (n=14) of women regularly visited family doctors and specialists. Having any physical health condition was most common among the suicide completers at age 50 to 70 years (53%, n=16/30) followed by those at age 30–50 years (37%, n=20/55), and lowest at age 18–30 years (24%, n=10/42). Cardiovascular system disorders (5.5%), metabolism or nutritional disorders (5.5%) were the most common followed by general or unspecified health problems (7.6%), musculoskeletal disorders (4.1%) and cancer (4.1%) (Table 3).

According to the data collected through interviews a lifetime history of diagnosed mental disorder have had reported in 29% (n=42) of suicide completers: 23% (n=26) of men, 47% (n=16) of women. More than a third (37%, n=54) of all suicide completers had history of mental disorders treatment with higher proportions for women (59%, n=20) than men (31%, n=34). The diagnosed mental disorders were treated and managed in several ways (Figure 2).



* p<0.005 men vs. women

Figure 2. **Reported treatment of mental disorders according to gender**

Medication use and visit to psychiatrist were more prevalent treatment of mental disorder with a higher proportion among women (40.6% and 37.5% respectively) then men (22.2% and 13% respectively).

The use of alcohol was reported in 50% (n=73) of all suicide completers. As reported, 14% (n=20) used alcohol on an irregular basis and 35% (n=50) on a regular basis. In line with the higher proportion of men suicide completers, the majority of alcohol users were men: 51% (n=57) of men vs. 44% (n=15) of women.

There is evidence that mental health may be associated by the use mental health services utilization. Over a third (32%, n=46) of all suicide completers were in contact with general practitioner 1-month prior their death, 9% (n=13) were admitted to a psychiatric hospital, while 10% (n=14) were referred for treatment to a psychiatric service.

DISCUSSION

This study analyzed of 145 adult suicide completers, who died by suicide during 2017–2019 years, using a psychosocial suicide autopsy method and interviewing relatives/acquaintances/friends or people who known well the suicide completers. Our pilot analysis is the one-dimensional trend that evaluates factors related to suicide as isolated and not as multiple, interacting factors. First, an initial analysis was performed according to frequency of variables, with the purpose of describing the studied sample.

Our study results presented sociodemographic characteristics of suicide very close to what is already known in the previous studies in Lithuania [9, 10, 11]. For example, gender is one of the most fre-quently replicated predictors for suicide; while rates of suicide in most countries are higher in males than females [12, 13].

In our study, among suicide completers female male ratio was 1:3. In most country men have higher rates than women, ranging from 3:1 to 7.5:1. According to data provided by the Institute of Hygiene in Lithuania, men are five times more likely to commit suicide than women [4]. Two exceptions are China and India, where suicide ratio are contrary: women have higher rates than men [14].

In our study women were significantly older than men. Among female suicide completers most were aged 18–30 (26%) and 70+ (26%) followed 41–50 (18%). Around two thirds (65%) of women were never married or widowed. The highest suicide risk is for middle-aged (45–59) and over 75 years old women [4]. Consistent with many (but not all) studies, lived alone and never married were found to be significant risk factors for the middle-aged suicides in our study [15–17].

In our study, women had a significantly higher prevalence of a history of suicide attempts than men. There are several possible explanations. First, women's greater vulnerability to suicidal behavior is likely to be due to gender related vulnerability to psychopathology and to psychosocial stressors [16]. Second, men choose more lethal method to commit suicide than women, while women tend to use self-poisoning for suicidal acts, which often have low lethality [18].

In our study, among suicide completers 30% of men and 26% of women were young adults aged 18 to 30 years, followed by middle-aged men (21%) and women aged 70+ (26%). Lithuanian statistics are similar – mostly suicide rates are in the middle age groups (35–54 years) and older age group (55–75 years). There were 29 suicides by young people aged under 25 (23 men, 6 women). These results are in line with previous studies indicating higher number of male committing suicide who was mid-aged and living in urban area [4]. This distribution according to age may be related to a nonlinear relationship between suicide risk and age. A separate analysis requires a middle-aged group.

Our study revealed, that both men and women share many experienced difficulties. The difficulties most commonly reported by interviewing relatives/friends of suicide completers by decreasing order of magnitude were: relationship problems, family conflicts and health problems were the most frequently reported life events associated with both men and women suicides. There were differences between men and women in terms of experienced difficulties, with financial problems and difficulties in work noted for men and bereavement and health problems for women.

Our study confirmed previous findings, that the most common method of suicide remains hanging, both for males and females [4, 19]. In our study, jumping/drowning was the second most common suicide method, whereas only eight men used firearm. Women were more likely to use jumping from a height, poisoning and drowning as suicide method. In general, men tend to choose more violent means (eg., hanging or shooting) and women less violent methods. (eg., self-poisoning) [18, 20].

According to our data half of those who committed suicide had a problem with alcohol. In line with the higher proportion of men suicide completers, the majority of alcohol users were men. McGirr and coworkers (2006) concluded that despite a lower prevalence of suicide among females, high levels of impulsivity and alcohol abuse appear to be valid risk factors for both genders [17]. The findings emphasize that more attention should be focused on evaluating alcohol use and the risk of alcohol dependence on suicide [21, 22].

The role of physical illness and life problems in contributing to suicide is potentially important with regard to suicide prevention. Mental disorders, greater social isolation, dealing with stressful life events, and having personality traits are associated with suicide risk, physical illness and functional impairment [23]. According to our data collected through interviews, nearly a third of all suicide completers could have mental health problems, and could be treated from mental disorders before death, and could be contacted to their family practitioner one month before death.

Case-control psychological autopsy studies have firmly established risk associated with some mental disorders including major depressive episodes and alcohol dependence [24] providing critical information for prevention efforts. The systematic review of Cavanagh et al. (2003) found thatthe mental disorders had the strongest associations with suicide [24]. The mental disorder, as currently defined, is a relatively homogeneous concept in most cultural groups but psychosocial factors are less so. Thus, reports of high relative and attributable risks associated with unemployment may be overestimates due to lack of controlling for the association with mental disorder [24, 25]. Nevertheless, that people rarely approach mental health professionals when faced

with difficulties in Lithuania [26] other authors suggest that im-proving the detection and treatment of all disorders, particularly in primary care, may be the most effective way of reducing suicide rates [24, 27].

This study provides crucial insights into suicide in Lithuania; strength of the study is large number of cases; however, our results should be considered and interpretation with caution given these limitations. First, the psychosocial autopsy method and necessary use of a proxy informant. All subjects were characterized used proxy-based interviews, family members of suicide completers were sources of information, therefore may bias results due to the shame and stigma around suicide deaths and other aspects. Second, the cross-sectional design of this study may not allow determination of causality. Third, the suicide completers in the study were not controlled with a healthy group. Our results cannot be generalized beyond our sample population.

CONCLUSION

Our results revealed differences among men and women in sociodemographic characteristics, and psychosocial factors. In summary, among suicide completers most were young adults of both genders aged 18 to 30 years, followed by middle-aged men and women aged 70+. The most prevalent perceived difficulties prior suicide, by decreasing order of magnitude, among men were interpersonal stressors, family conflicts, problems in work and financial difficulties, while among women were health problems, and bereavement. Among suicide completers, compare with men, a higher proportion of women: were widowed, experienced a history of suicide attempts, had health problems, mental disorders treatment by medication use and regularly visited family doctors and other specialists. Subjects of both genders had history of committed suicide in their family, but a higher proportion of men suffered from drug and alcohol abuse.

These data provide scientific knowledge on gender differences of suicide completers in different socio-cultural contexts, and may be useful for suicide prevention oriented to gender.

ACKNOWLEDGEMENTS

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The Effect of Elicited Emotional States on Women's Reaction to Food Cues

Sukeltų emocinių būsenų poveikis moterų reakcijai į maisto užuominas

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SUMMARY

Purpose. This study aimed to investigate the effect of elicited emotional states on women's reaction to food cues.

Methods. 87 women (aged 20–39) participated in the study. The study used experimental design, in which reaction times to food cues were measured before and after randomly assigned experimental mood induction group (negative, positive or control). Reaction time to food cues and attention bias were measured using visual dot-probe task (stimuli exposure duration was 500 ms). Before experiment the psychological eating styles (measured by Three-Factor Eating Questionnaire-R21) and demographic characteristics were assessed. The data was analyzed using univariate and bivariate methods as well as logistic regression analysis.

Results. Logistic regression analysis showed that mood induction did not account for changes in attention bias or reaction times among study participants. Yet, the reaction time to food cues after mood induction decreased in all experimental groups, while attention bias to food cues decreased after mood induction in negative and positive mood induction groups.

Conclusions. The current study revealed that negative and positive emotional states do not affect women's reaction to food cues or attention bias to food stimuli as measured through visual dot-probe task.

Keywords. attention bias, mood induction, emotional eating, food cues, visual dot-probe task

SANTRAUKA

Tikslas. Tyrimu buvo siekiama nustatyti sukeltų emocinių būsenų poveikį moterų reakcijai į maisto užuominas.

Metodai. Tyrime dalyvavo 87 20–39 metų moterys. Atliktas eksperimentinis tyrimas, kurio metu reakcijos laikas į maisto užuominas buvo matuotas prieš ir po atsitiktiniu būdu paskirtos emocinės būsenos sukėlimo užduoties (negatyvi, pozityvi ar kontrolinė). Reakcijos laikas į maisto užuominas ir dėmesio tendencingumas matuotas vizualinio zondo užduotimi (stimulai rodomi po 500 ms). Prieš eksperimentą apklausos būdu įvertinti tiriamųjų psichologiniai mitybos stiliai (angl. *Three-Factor Eating Questionnaire-R21*) ir demografinės charakteristikos. Duomenys analizuoti naudojant vienmatę, dvimatę analizes ir logistinės regresijos modelius.

Rezultatai. Logistinės regresijos modeliai atskleidė, kad sukeltos emocinės būsenos neturėjo poveikio dėmesio tendencingumo ir reakcijos į maisto užuominas pokyčiams. Nepaisant to, reakcijos laikas į maisto užuominas po emocinės būsenos sukėlimo užduoties sumažėjo visose tyrimo grupėse, o dėmesio tendencingumas po užduoties sumažėjo negatyvaus ir pozityvaus poveikio grupėse.

Išvados. Negatyvios ir pozityvios emocinės būsenos neturėjo poveikio moterų reakcijai į maisto užuominas ir dėmesio tendencingumui į maisto stimulus, matuojant vizualinio zondo užduotimi.

Raktažodžiai. Dėmesio tendencingumas, emocinės būsenos sukėlimas, emocinis valgymas, mityba, vizualinio zondo užduotis

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INTRODUCTION

Over the last few decades, obesity has become a major global heath challenge [1]. The prevalence of overweight and obesity is quickly rising and is considered to affect up to 38 percent of adults globally [1]. Obesity negatively impacts health – it is linked to cardiometabolic diseases, type 2 diabetes, coronary artery disease [2-3], and is also involved in the majority of the leading causes of death [4]. One of the main causes of obesity is increased energy consumption [5] though other factors are also playing a role. Thus, it is important to investigate contributing factors to overeating and obesity, especially the lesser researched ones like cognitive factors, particularly attention bias (AB) [6].

AB is a selective information processing in which individuals direct their attention towards personally relevant stimuli, when neutral stimuli are also present [7]. Detecting and approaching food in the environment is considered to be one of the most essential evolutionary adaptations for survival [8], therefore elevated AB for food can be prevalent in people with normal body mass index (BMI), especially while feeling hungry [9]. However, higher AB can predict weight gain [10] and faster reaction times for food are associated with higher BMI [11, 12].

Eating is not always regulated by objective states like feelings of hunger or satiety; it can also be used as an emotion regulation strategy [13]. Emotions can direct behavior by influencing different cognitive processes [14], that can direct attention towards personally attractive incentives that could potentially change a person's mood in a positive way, either by enhancing positive affect or by reducing negative affect [15]. Several studies have studied the association between AB for food and emotion. Research shows that sad mood increases attention to unhealthy food in women with food addiction [16], increases AB after negative mood between students [17, 18]. However, some studies have found that negative emotions do not have any effect on AB [19, 20].

However, studies that examined if elicited emotions have an effect on AB are scarce [16-20] and a lot is still unknown about this relationship. Previous studies have concentrated on negative emotions and their effect on AB. There is no research about relationship between positive emotions and AB, even though it is known that positive emotions increase food consumption as much as negative emotions do [21]. Therefore, the aim of this study was to examine the effect of elicited emotional states on women's reaction to food cues. In this experiment we included negative and positive emotional states, so that we could compare how different emotional states affect the reaction times and AB for food.

METHODS

Participants

A total of 87 women were included in the study. Participants were recruited through flyers shared in public places of Kaunas city and online through various social media groups. Participants' age ranged from 20 to 39 due to the fact that they have passed puberty but not yet experienced the effects of hormonal decline [22]. The exclusion criteria were: current occurrence of severe depression and anxiety symptoms (measured by Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7)) and various dietary restrictions (like vegetarian, vegan diets).

The study was conducted in accordance with ethics approval by the Lithuanian University of Health Sciences Ethics Committee (reference No. BEC-SP(M)-49).

Participants were randomly assigned to one of the three experimental groups: neutral, negative or positive mood condition (N=29 in each). The mean age of participants was 26.5±6.11 years. The sample's mean body mass index was within normal range (22.3±3.37).

Procedures

Mood induction

Video clips were used to induce a respective emotional state in different experimental groups. The video for neutral mood induction (MI) group was taken from the movie "Strangers on a Train"; negative MI group watched a scene from the movie "Hereditary"; positive MI group watcher a scene from short film "Merci!". All video clips were shown from a video-sharing website YouTube, their length varied from two to five minutes, as it is considered to successfully induce emotional states [23], making it an easy and ecologically valid method to induce emotional states [24].

Visual dot probe task

To assess reaction times and attention bias for food, manual response latencies were recorded during a visual dot probe task. During this task two pictorial stimuli appear simultaneously on the left and right sides of a computer screen, followed by a probe (a small dot) that replaces one of the stimuli. Participants are instructed to respond as quickly as possible to the location of the dot by pressing a corresponding key on the keyboard. If the attention is automatically drawn towards personally more important stimulus, the responding time to the dot that replaces the image is faster [25].

Each trial started with a fixation cross (that disappeared after 500 ms), followed by a stimulus pair (shown for 500 ms). Then the probe appeared and stayed on the screen until participants made a manual response indicating the position of the probe. The probe equally often replaced food and neutral stimuli and was equally distributed on the right and left screen locations. The task consisted of 120 trials, with 80 critical trials (photograph of sweet high-caloric food stimulus paired with a photograph of a neutral stimulus) and 40 filler trials (two neutral stimuli). All photographs were taken from "Food-pics" database [26].

Following previous research [e.g. 20], response latencies faster than 200 ms, slower than 2000 ms or more than 3 SDs above each participant's mean were excluded from the analysis. AB scores were calculated by subtracting the mean response latency on congruent trials (when the probe replaced food stimulus in critical trials) from the mean response latency on incongruent trials (when the probe replaced neutral stimulus in critical trials). A positive bias score was indicative for an AB towards food stimuli, whereas a negative bias score can be interpreted as attention avoidance from food stimuli.

Procedure

Before the experimental procedure, participants completed the questionnaire which included TFEQ-R21, demographic characteristics and exclusion criteria. Participants that were eligible for the study were invited to Lithuanian University

of Health Sciences Public Health laboratory, where the experiment took place. All the participants were tested individually by one experimenter.

Upon arrival, the participants signed the informed consent form and filled in the visual analogue scale (VAS) for subjective hunger. After that all the participants completed first measure of visual dot probe task. Then, participants rated their emotional state before MI (VAS1). Depending on the experimental group that the participants were randomly assigned to, they watched a negative, positive or neutral video clip and subsequently rated their emotional state after MI (VAS2). Finally, participants completed another visual dot-probe task. At the end of the experiment participants were debriefed.

Measurements

Visual analogues scale (VAS) was used to measure subjective hunger (at baseline) and emotional states (before and after MI). Each scale consisted of a continuous line ranging from 0 ("very bad mood"; "starving") to 10 ("very good mood"; "full"). Emotional states were not labeled due to the fact that seeing emotional adjectives can change how a participant feels [27]. Participants were asked to mark a cross on each line to indicate how they were feeling.

The Three Factor Eating Questionnaire-R21 (TFEQ-R21) [28]: a 21-item questionnaire with three scales: emotional eating (6 items; α=0.939), uncontrolled eating (9 items; α=0.882), cognitive restraint (6 items; α=0.759). Items were scored on a four-point Likert scale ranging from "definitely true" to "definitely false". Possible scores range from 0 to 100 with higher scores indicating greater prevalence.

Demographic characteristics: participants were asked about their age, education, height and weight. Height and weight were used to calculate BMI, which was later grouped into three categories: low (<18.5), normal (18.5 to 24.99) and high (25.0 and more) [29].

Analyses

Statistical analyses were performed using "IBM SPSS Statistical Version 23". Statistical significance level was set at $p<0.05$.

Because data between groups was not normally distributed, non-parametric methods were used. Spearman correlation was used to compute associations between variables under study; Kruskal-Wallis test was used to compare three independent experimental groups; Wilcoxon signed-rank test was used to compare two related samples.

Multivariate logistic regressions were used to determine whether MI procedure had an effect on reaction time and AB for food. The regression method was used to determine how different factors (MI, psychological eating styles, BMI and age) associated with AB and reaction times to food cues. Odds ratios (OR) and 95% confidence intervals for each independent variable in the model were computed.

RESULTS

Group characteristics

Independent sample Kruskal-Wallis tests confirmed that there were no significant differences between different experimental groups, except for the difference in measurement of time since last meal (p=0.034; Table 1). Even though participants in different experimental groups differed from one another by the time since they last ate, the subjective hunger did not differ significantly. Thus, participants in all

Table 1. **Characteristics of study participants (n=87)**

Variables	Mean±SD or N (%)			
	Neutral	Negative	Positive	p
Education				
Secondary	9 (31)	13 (44.8)	10 (34.5)	0.269
Vocational	0 (0)	3 (10.3)	2 (6.9)	
Higher	20 (69)	13 (44.8)	17 (58.6)	
Body mass index (BMI)				
Low	1 (3.4)	1 (3.4)	3 (10.3)	0.685
Normal	20 (69)	23 (79.3)	20 (69)	
High	8 (27.6)	5 (17.2)	6 (20.7)	
Age	26.5±5.78	25.7±5.85	27.1±6.79	0.726
Hunger at baseline	7.72±2.52	6.95±2.95	7.86±2.63	0.348
Time since last meal (h)	3.64±4.62	3.71±3.38	2.03±2.00	0.034
TFEQ-R21				
Emotional eating	35.3±29.70	34.5±31.19	36.1±29.57	0.982
Uncontrolled eating	37.8±16.79	42.0±25.73	38.0±24.90	0.778
Cognitive restraint	46.6±19.47	36.2±22.87	39.3±22.2	0.156
VAS				
Mood at baseline	7.1±2.07	7.5±1.43	6.9±2.24	0.918
Mood after MI	7.3±1.75	4.6±2.18	8.2±1.77	<0.001
Reaction time pre-MI (ms)	414.0±48.54	442.9±121.75	442.8±74.96	0.428
Reaction time post MI (ms)	398.2±45.23	420.2±89.37	412.5±43.74	0.428
Attention bias pre-MI	8.3±11.85	7.5±17.23	6.7±14.46	0.851
Attention bias post MI	2.3±11.97	-2.8±13.86	-1.3±8.95	0.431

Note: TFEQ-R21 – The three-factor eating questionnaire revised 21; VAS – visual analogue scale, MI – mood induction.

the experimental groups arrived in a similar mood and hunger states for the experiment.

Mood induction

First, we measured the effectiveness of completed MI procedure, using Wilcoxon signed-rank test. Results showed significant interactions between MI and time: after the MI procedure, subjective mood in negative experimental condition significantly decreased ($p<0.001$), in positive condition significantly increased ($p<0.001$), and did not significantly change in neutral condition ($p=0.109$) (Fig. 1). The differences between groups after MI were statistically significant ($p<0.001$; Table 1).

Reaction time to food and attention bias

We tested changes in reaction times and AB for food stimuli after MI in different experimental conditions. Results suggest that reaction time in all experimental conditions significantly decreased (neutral condition $p=0.007$; negative condition $p=0.005$; positive condition $p<0.001$; Fig. 2). Results for AB score showed statistically significant decrease after MI in negative and positive experimental conditions ($p=0.024$, $p=0.005$ respectively). AB also decreased in neutral condition but the result was not significant ($p=0.071$; Fig. 3). There were no significant differences between the experimental groups in reaction time and AB before or after MI (Table 1).

The effect of mood induction on reaction time and attention bias

We conducted and analysis to see if elicited emotional states had an effect on reaction time and AB.

First, we examined correlations between reaction time, AB and psychosocial variables under study (Table 2). The results showed that reaction time moderately correlated with age ($\rho=0.49$), weakly correlated with body mass index ($\rho=0.33$) and uncontrolled eating ($\rho=0.29$). We did not find any significant correlations between AB and psychosocial variables under study.

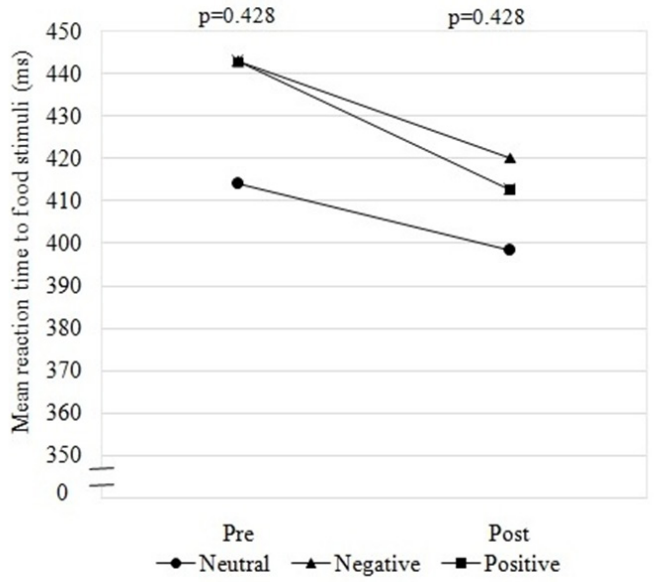

Figure 2. **Mean reaction time to food stimuli (ms) per experimental condition before and after MI**

Next, we conducted two multivariate logistic regression analyses in order to identify factors that could affect reaction time and AB for food (dependent variables). Independent variables were chosen by significance level $p\leq0.2$ [30].

While analyzing what factors influenced reaction time to food after MI, dependent variable (reaction time after MI) was split using median value (50 percentile; 394.9) as a cut off point for dichotomization. Independent variables included in the model were experimental condition, reaction time before MI, uncontrolled eating, BMI and age. Multivariate logistic regression showed that reaction time before MI was significantly predicted by reaction time before MI (OR=1.06) controlled by experimental condition, uncontrolled eating, BMI and age (Table 3).

Finally, we analyzed what factors influenced AB after MI. Dependent variable (AB after MI) was split into two groups

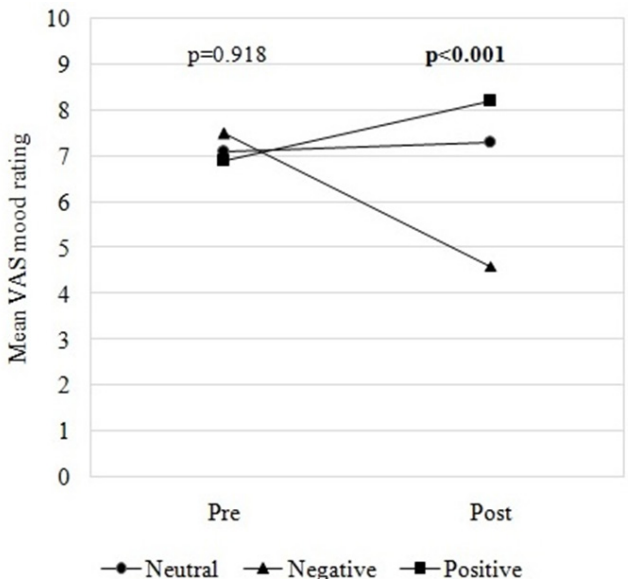

Figure 1. **Mean mood ratings per experimental condition before and after MI**

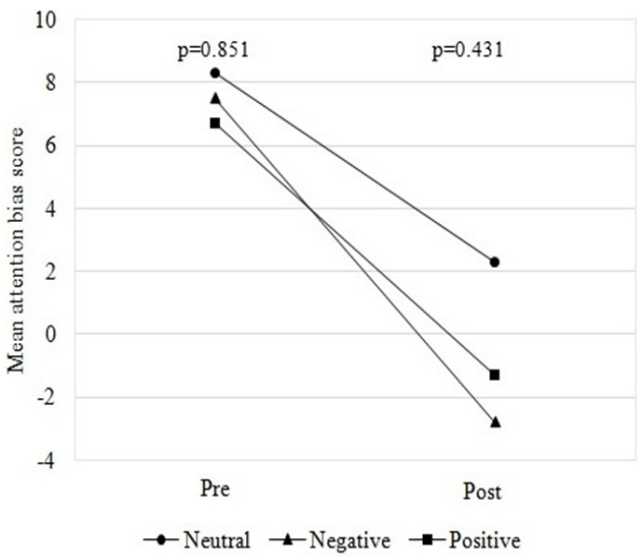

Figure 3. **Mean attention bias to food stimuli score per experimental condition before and after MI**

Table 2. **Spearman correlations between reaction time, attention bias and dietary and demographic indicators**

	Reaction time post MI	Attention bias post MI
Uncontrolled eating	0.29*	-0.09
Cognitive restraint	0.10	0.08
Emotional eating	0.11	-0.05
Subjective hunger	0.06	0.09
BMI	0.33*	0.03
Age	0.49**	0.08

Note: *p<0.05, **p<0.001; MI – mood induction, BMI – body mass index

for dichotomization: negative AB (<0) and positive AB (>0). Independent variables included in the model were experimental condition and AB before MI. Multivariate logistic regression model showed no significant factors predicting AB after MI (Table 4).

DISCUSSION

This experimental study has been conducted and the results indicate that emotional states, either positive or negative, did not affect reaction times to food cues or attention bias to food in the current sample as measured by dot-probe task.

Despite the fact that emotional states did not affect the reaction times or AB, these indicators did significantly change after mood induction. After MI, reaction time decreased in all experimental conditions, while AB decreased in negative and positive experimental groups. After MI, participants in negative and positive experimental conditions reacted faster to neutral stimuli compared to food stimuli, showing attentional avoidance to food [25]. As the stimuli in the dot-probe task were shown for 500 ms, they reflect conscious aspects of attention. It can be hypothesized that people after MI consciously relocated their attention from food to neutral stimuli. Avoidance helps when a person does not have adequate resources to process information [25]. In negative experimental group that could have happened because negative emotions tend to reduce reward value, leaving people less motivated to search their surroundings for motivational stimuli [31]. Positive emotions could leave people less motivated to search for salient stimuli because they already feel content with their emotional state and do not feel the need to make it better.

Table 3. **Factors predicting attention bias after MI: multivariate logistic regression**

Indicator	Group	Attention bias after MI OR (95% CI)	p
Experimental condition	Neutral	1.00	
	Negative	0.88 (0.31–2.50)	0.810
	Positive	0.78 (0.27–2.22)	0.640
Attention bias before MI		1.02 (0.99–1.05)	0.169

Note: MI – mood induction, OR – odds ratio, CI – confidence intervals

Table 4. **Factors predicting reaction time to food cues after MI: multivariate logistic regression**

Indicator	Group	Reaction time after MI OR (95% CI)	p
Experimental condition	Neutral	1.00	
	Negative	0.51 (0.08–3.35)	0.480
	Positive	1.14 (0.20–6.55)	0.886
Reaction time before MI		1.06 (1.03–1.09)	<0.001
Uncontrolled eating		1.03 (0.99–1.07)	0.096
BMI		0.95 (0.73–1.22)	0.666
Age		1.04 (0.88–1.24)	0.643

Note: MI – mood induction, BMI – body mass index, OR – odds ratio, CI – confidence intervals

Prior research on this topic has found mixed results. In study conducted by Werthmann and colleagues [20] negative mood induction decreased initial orientation towards food. Hepworth and colleagues [17] aimed to examine the effect of negative mood on attentional bias between women students. They found that negative mood increased AB, meaning that women reacted faster to food stimuli compared to neutral stimuli. These mixed results could come from different assessment of attention bias: our study used visual dot-probe task with stimuli present for 500 ms. Similarly, Hepworth and colleagues used a visual dot-probe, but stimuli were present for 500 ms and 2000 ms, analyzing different components of attention; while Werthmann and colleagues measured the AB with eye movement recordings.

Our study did not find prognostic variables for attention bias or reaction times to food cues. Previous research also did not provide consistent results. Some researchers find correlations between AB and external eating [32, 33], or trait impulsivity [32]. In the above-mentioned study by Werthmann [20], emotional eating did not predict changes in attention allocation for food. It can be hypothesized that emotional states are not sufficient for changes in reaction to food to occur. It is thought that emotion regulation strategies, impulsivity or self-control levels could have a bigger impact in this relationship. For example, Pollert and Veilleux [34] found that AB predicted eating behavior after self-control exertion. Other study by Schepers and Markus [18] has found that both genetic and cognitive stress vulnerability increased AB for high palatable food during acute stress.

Our study also had some limitations. First, the question concerning the visual dot-probe task and its validity needs to be addressed. Even though this technique has been widely used to measure AB in different populations [7, 35], studies on its validity are very rare. Some researchers find the task to be reliable [36], while other studies report low reliability [37, 38].There are also some questions about the tasks' ecological validity. The participant's in our experiment reported feeling bored and finding it hard to concentrate while completing the task for the second time at retest. The second limitation would be the fact that sweet high calorie food images were chosen as food cues in the experiment. While these stimuli are more

likely to catch attention [39], they could have been personally irrelevant for some of the participants.

Despite these potential limitations, one of the biggest strengths of our study includes its experimental design, involving negative, positive emotional states and a neutral control group. This experimental design enabled us to draw implications about the effect that study variables had on AB. Finally, our research concentrated on a wider population, not limiting itself on students as other previous studies in this field usually practiced [17, 20].

These strengths and limitations raise some recommendations for future studies. First, it raises the need for a new and ecologically valid measure of AB. Finding a way to measure AB in real life situations would show the real impact of AB on eating behavior. One of more successful methods to do that is eye tracking technology [20]. Another important thing to investigate would be how AB impacts the feeling of hunger and consequently eating behavior.

To conclude, we can state that the current study revealed that negative and positive emotional states do not affect women's reaction to food cues or attention bias to food stimuli as measured by visual dot-probe test.

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The association between women loss of reproduction capacity and depressive disorder: a selective literature review

Reprodukcinių savybių praradimo sąsaja su depresiniu sutrikimu: selektyvi literatūros apžvalga

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SUMMARY

Infertility is a disease of the reproductive system defined as the inability to reach clinical pregnancy for 12 months or more through regular sexual intercourse without using protection. It is well known that for most women, failure to conceive a child is the most difficult emotional experience. The risk is exacerbated by the public perception that infertility is caused by women, especially in developed countries, where having children is important for religious, social, cultural and economic reasons. Therefore, infertility can affect their social, physical and psychological well-being and lead to social isolation. Infertile patients often complain of stress and affective disorders, of which anxiety and depressive disorders (because of the infertility or infertility treatment) are the most common.

Key words: infertility, depression, anxiety, assisted reproductive technology, infertility treatment

SANTRAUKA

Reprodukcinių savybių praradimas (nevaisingumas) – tai reprodukcinės sistemos liga, apibrėžiama kaip nesugebėjimas pasiekti klinikinio nėštumo 12 ir daugiau mėnesių reguliarių lytinių santykių metu, nenaudojant apsauginių priemonių. Gerai žinoma, kad daugumai moterų negebėjimas pastoti ir pagimdyti vaiką – sunkiausias emocinis išgyvenimas. Riziką didina visuomenės suvokimas, kad negalėjimas susilauti vaiko kyla dėl moters kaltės, ypač išsivysčiusiose šalyse, kur vaikų turėjimas yra svarbus dėl religinių, socialinių, kultūrinių ir ekonominių priežasčių. Dėl šių priežasčių nevaisingumas turi įtakos moters socialinei, fizinei ir psichologinei savijautai bei gali sukelti socialinę izoliaciją. Nevaisingos pacientės dažnai skundžiasi streso bei afektiniais sutrikimais, iš kurių dažniausi yra nerimo ir depresinis (sukeltas nevaisingumo ar nevaisingumo gydymo) sutrikimas.

Raktiniai žodžiai. Nevaisingumas, depresija, nerimas, pagalbinis apvaisinimas, neivaisingumo gydymas

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INTRODUCTION

Infertility is a condition of the reproductive system, defined as the inability to achieve clinical pregnancy for 12 months or more during regular sexual intercourse without the use of protective measures. It is divided into primary, when there have been no previous pregnancies, and secondary, when there has been at least one successful, uninterrupted pregnancy [1]. According to PSO global study in 2012 (190 countries and their territories were involved), 48.5 million couples were affected by infertility in 2010. 14.4 million of these couples live in South Asia, and further 10.0 mln. live in Sub-Saharan Africa. In Central/Eastern Europe and Central Asia, the number of infertile couples is looking for 3.8mln. [2]. Infertility affects about 10–15% couples or approximately every seventh couple [3]. In Lithuania in 2018, the number of infertile women per 1,000 population reached 1.59, men – 0.13 [4]. In most cases, couples learn about infertility only after long-term attempts to conceive.

Although infertility is considered a stressful situation for a couple, women still experience more stress than men [5]. For most women, the inability to give birth is the most difficult emotional experience, causing the same level of psychological stress as a person with oncological or ischemic heart disease [6]. Studies examining gender differences in psychological adjustment to infertility have found that women in such traumatic situations are at higher risk of developing mental disorders [7]. The risk is exacerbated by the public perception that infertility is caused by women, especially in developed countries, where having children is important for religious, social, cultural and economic reasons [8]. Therefore, infertility can affect their social, physical and psychological well-being and lead to social isolation.

Depressive disorder is one of the most common mental health disorders in infertile women, primarily due to loss of reproductive traits, as well as stressful assisted reproduction procedures and adverse outcomes of assisted reproduction procedures [9].

The increasing prevalence of infertility in society and the negative impact on psychological and social well-being have led us to review the links between infertility, infertility treatment, and depressive disorder

The objective of the present report was to review the association between infertility, infertility treatment, and depressive disorder based on national and international literature.

METHODS

MEDLINE/PubMed was searched for the period 2015–2020 for english-language studies using the following key terms: infertility, depression, anxiety, assisted reproductive technology, infertility treatment. Open and randomized controlled trials, original observational studies, case reports, case series, and reviews were included. Initial search with key words returned n = 515 of which n = 467 did not match inclusion criteria: full text articles, female participants, age ≥18 years old. So, 48 articles were included into this literature review.

RESULTS

Causes of infertility

Fertility is affected by several factors: age, acute or chronic illness, environmental pollution, occupational factors, harmful habits, infectious diseases, genetic conditions, and specific reproductive disorders that can affect a man or woman trying to conceive.

According to a World Health Organization (WHO) study, of the 8,500 infertile couples studied in developed countries, found: female infertility, 37%; male infertility, 8%; both female and male infertility, 35%. The infertility of the remaining pairs was not elucidated or abstained during the fetal study [10]. A more detailed analysis highlights the following specific causes of infertility in women [11]: ovulation disorders – 25%, endometriosis – 15%, abdominal adhesions – 12%, tubal obstruction – 11%, other tubal lesions – 11%, unclear. Infertility of 10%, other causes – 9%, hyperprolactinemia – ≥ 7% [12].

Age is one of the most significant risk factors for infertility. It has been shown that a woman's chances of getting pregnant decrease with age. Not only is the number of oocytes decreasing, but the remaining oocytes are of poorer quality, which increases the incidence of chromosomal diseases and the likelihood of spontaneous abortions [13]. Women as they age also face an increased risk of developing disorders that lead to infertility, such as endometriosis, leiomyoma, or tubal disease [14]. Women undergoing oligo-ovulation or anovulation have difficulty becoming pregnant because the oocyte does not mature every month for fertilization. The most common cause of anovulation is polycystic ovary syndrome (POS) [15]. However, ovulation disorders can also occur for other reasons: hypothalamic-pituitary axis pathology, which can be caused by intense, inadequate exercise, eating disorders, hyperprolactinemia, autoimmune disease, etc. [16].

Mechanisms by which depression, anxiety, and emotional distress may contribute to infertility include hypothalamic – pituitary – adrenal (HPA) axis dysregulation [17], gonadotropin – releasing hormone (GnRH) pulse suppression [18], and autonomic nervous system activation [19]. Secondary effects of depression and anxiety on general health and diet can also lead to infertility. In addition, depression may reduce women's motivation to continue infertility treatment after treatment failure. Unfortunately, the evidence investigating the link between infertility and depression or anxiety is not complete. The meta-analysis done by Matthiesen et al. (2011) have found that stress and anxiety were associated with lower clinical pregnancy rates in women undergoing infertility treatment [20], but Boivin et al. (2011) meta-analysis have not found such association [21]. A large prospective study by Zaig et al. (2012) of women who underwent their first in vitro fertilization showed that the percentage of successful pregnancies was similar among women with or without mental symptoms or diagnoses [22].

Thus, depression can be not only the cause or consequence of infertility, but also as a consequence of failed infertility treatment.

Depression as a consequence of infertility

Is still unclear whether infertility is a consequence or cause of depression. Although the term "psychogenic infertility" is

being phased out, with all medically unexplained infertility attributed to psychological causes, many infertile women believe that the emotional stress they experience contributes to their continued infertility.

Infertility causes psychological, marital, and social phenomena of distress, including depression, stigma, sexual dysfunction, marital dissatisfaction, and withdrawal from family or friends [23]. Infertile patients often complain of stress and adaptation disorders, of which anxiety and depression are the most common [24]. Depression is a common reaction to infertility, often resulting from loss of identity, incompetence, or a sense of social stigma [25]. Infertility also particularly affects women, who are most often blamed for it [26] and affects many aspects of their lives, such as social, physical and psychological well-being [27]. In addition, a woman may lose a close relationship with her partner, a status in society, develop a low self-esteem, may lose hope for the future, and these feelings may lead to depression [28].

The ICD-10 classification identifies three main symptoms of depression: persistent sadness or low mood and / or loss of interests or pleasures and fatigue or low energy. The are also other seven associated symptoms but they are not main. These symptoms should last for at least 2 weeks [29].

Despite the high prevalence of infertility, infertile women do not share their infertility history with family or friends, thus increasing their psychological vulnerability. The inability to reproduce naturally can lead to feelings of shame, guilt and low self-esteem. These negative feelings can lead to varying degrees of depression, anxiety, suffering, and impaired quality of life [30].

The prevalence of depression among infertile women varies from 8% to 54%. Depression is considered to be one of the major health problems associated with infertility, especially in developing countries, where having a child is crucial for socio-cultural, economic, and religious reasons. Jasim et al. study found that depression was prevalent in 68.9% of the population in Iraq. Of women with depression, 42.2% had mild depression, 50.3%. – moderate depression, and only 7.5% – major depression. The analysis showed that the duration of infertility longer than 5 years was significantly associated with depression. Primary infertility was also found to be significantly associated with depression (95%). Other variables found such as duration of treatment and men's threat to another marriage were significantly associated with depression. All other variables studied did not show a significant association with depression [25]. Several studies have identified factors associated with depression and / or anxiety in infertile women. Domar et al. found that depression peaked in the third year after infertility diagnosis [31]. Matsubayashi et al. performed psychological tests on infertile women and healthy pregnant women. They found that infertile women had significantly higher psychological stress scores [32]. The study also found that anxiety and depression are caused by a lack of male support for an infertile woman [33]. In another Ramezanzadeh et al. study conducted in 2006 (n = 370), 86.8% of infertile women had symptoms of anxiety and 40.8% of women suffered from depression. An association between anxiety, depression and the duration of infertility has been identified with the greatest occurrence occurring 4 to 6 years after the diagnosis of infertility [34]. Another study in Vietnam involved 401 women. This study found that depression was more common in infertile women than in the general Vietnamese population [35]. However, this prevalence was lower than the prevalence of depression among infertile women in other populations, as found by Lok et al. [36], Fatemeh et al. [37] and Al Homaidan [38] (prevalence was 33%, 40.8%, and 53.8%, respectively).

Kanclerytė et al. conducted a study in Lithuania, which examined the emotional state of 107 infertile women. The results of the study showed that 68.6% of participants had symptoms of anxiety and 21% of women suffered from depression. Also there was no statistically significant ($p > 0.05$) difference in the prevalence of anxiety and depression according to age, marital status, co-morbidities and possession of harmful habits. However, although insignificant, the results show that anxiety was more pronounced in younger patients and depression more common occurred among older women. [39]

Thus, infertile women experience distress that includes social stress, depression, sexual dysfunction, and dissatisfaction with marriage [40]. However, it should be noted that psychological symptoms can be caused not only by the diagnosis of infertility but also by the failure of infertility treatment.

Depression as a consequence of infertility treatment

Recently, much attention has been paid to the relationship between infertility treatment using artificial insemination methods and the onset of mental disorders, most commonly anxiety and depression [41]. In 2011 Mariko Ogawa et al. conducted a study involving 83 Japanese women who were examined and treated for infertility at the Tokyo Reproduction Center at Ichikawa General Hospital College of Dentistry from February to April 2018. The psychological status of women was assessed by several tests: the Self-rating Depression Scale (SSD) and the Hospital Anxiety and Depression Scale (HADS). The results of the study revealed that patients treated for infertility had higher HADS depression scores compared to patients who were not treated [42]. Other studies have found that more than half of all infertile women describe infertility treatment as "the most stressful experience of their lives" [43, 44]. In women undergoing infertility treatment, major depressive disorder (MDD) is as high as 17% to 19.5% [45]. Medications used to treat infertility, including clomiphene, leuprolide, and gonadotropins, have also been linked to psychological symptoms such as anxiety, depression, and irritability. Therefore, going halfway through treatment, it is difficult to distinguish whether psychological symptoms are caused by infertility or whether it is a side effect of medication. The longer a patient is treated, the more often symptoms of depression and anxiety occur.

Nearly 40% of couples treated for infertility were still unable to conceive [46]. Patients who had one treatment failure had significantly more pronounced symptoms of anxiety and patients who experienced two failure had significantly more pronounced depressive symptoms compared with patients who did not receive infertility treatment [47]. Little Lund et al. study showed that 15% of women whose infertility treatment did not end in pregnancy suffered from major depression [45]. It has been found that distress can last up to 20 years after unsuccessful infertility treatment [48]. Patients undergoing

fertility treatment are at high risk for mental disorders, so it is important to recognize them in a time, help patients to deal with them and help them cope.

CONCLUSIONS

Depression is one of the major clinical problems faced by women diagnosed with infertility. As the duration of infertility increases, the incidence of depression increases. Ineffective treatment of infertility is one of the risk factors for the development of depressive disorder. It has been observed that patients with infertility have been diagnosed with a more severe degree of depression compared with women who have received specialized psychological care. Thus, infertile women should be counseled and supported throughout the treatment process, as psychological support for these women can prevent depression or reduce its symptoms.

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The role of testosterone in clinical manifestation of mental disorders and type 2 diabetes: a literature review

Testosterono vaidmuo psichikos sutrikimų ir 2 tipo cukrinio diabeto klinikoje: literatūros apžvalga

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SUMMARY

Introduction. Testosterone is one of the major circulating androgens in the human body. Studies on testosterone have shown that testosterone plays an important role not only in pathogenesis of various somatic diseases, e.g. type 2 diabetes, but is also important of the development of mental disorders – anxiety, depression and neurodegenerative disorders. In this article we will review the effect of testosterone in manifestation and treatment of disorders, including mental disorders.

Aim. To review the experience of clinical trials and the most relevant study data between testosterone and the development of anxiety, depression, neurodegenerative disorders and type 2 diabetes and the role of testosterone therapy as an option to manage these disorders.

Methods. Literature search was performed using OWID (ourworldindata.org) statistics and research published in the PubMed database , that reviewed the role of testosterone in the development and management of mental, neurodegenerative disorders and type 2 diabetes.

Results. Augmentation of primary drugs with testosterone or testosterone replacement therapy could be used to treat anxiety, depression, neurodegenerative disorders or type 2 diabetes in some groups that meet narrow criteria, but the results of some studies remain controversial. To ensure safety of treatment augmentation with testosterone replacement therapy extensive long-term controlled clinical trials are still required.

Keywords: testosterone, anxiety, depression, type 2 diabetes, neurodegenerative disorders

SANTRAUKA

Ivadas. Testosteronas yra vienas iš pagrindinių androgenų, cirkuliuojančių žmogaus organizme. Atliekant tyrimus susijusius su testosteronu pastebėta šio hormono svarba ne tik įvairių somatinių ligų, tokių kaip 2 tipo cukrinis diabetas patogenezėje, bet ir psichikos sutrikimų – nerimo, depresijos, neurodegeneracinių ligų išsivystymui. Šiame straipsnyje apžvelgsime testosterono poveikį sutrikimų pasireiškimui bei gydymui, įskaitant ir psichikos sutrikimus.

Tikslas. Apžvelgti klinikinių tyrimų patirtis bei aktualiausius literatūros duomenis apie testosterono sąsajas su psichikos sutrikimų, tokių kaip nerimo, depresijos, neurodegeneracinių ligų bei 2 tipo cukrinio diabeto išsivystymui bei galimą testosterono vaidmenį šių ligų valdyme bei gydyme.

Metodai. Literatūros apžvalga buvo atlikta naudojantis OWID statistiniais duomenimis (ourworldindata.org) ir paieška PubMed duomenų bazėje pateiktais tyrimais bei apžvalginiais straipsniais apie testosterono vaidmenį psichikos sutrikimų, neurodegeneracinių ligų, 2 tipo cukrinio diabeto išsivystyme bei jų valdyme.

Rezultatai. Pagrindinio medikamentinio gydymo augmentacija testosteronu galėtų būti naudojama nerimo, depresijos, neurodegeneracinių ligų arba 2 tipo cukrinio diabeto gydyme, tačiau dalies tyrimų rezultatai išlieka kontraversiški. Tam, kad būtų saugu naudoti testosterono pakaitinę terapiją augmentuojant ligų gydymą, dėl didelės nepageidaujamo poveikio tikimybės yra reikalingi didesnių apimčių ilgalaikiai kontroliuojami klinikiniai tyrimai.

Raktiniai žodžiai: testosteronas, nerimas, depresija, 2 tipo cukrinis diabetas, neurodegeneracinės ligos

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INTRODUCTION

Testosterone, also known as a primary sex hormone, anabolic steroid in males or an androgen, by chemical structure is a 19-carbon steroidal derivative of cholesterol. First, cholesterol is converted to pregnenolone within mitochondria by the side-chain cleavage enzyme (P450scc). After that, by other P450 enzymes pregnenolone is converted to a different androgens [e.g., dehydroepiandrosterone (DHEA) and androstenedione]. In the human population the dominant circulating androgen is testosterone [1, 2]. Leydig cells of the testes produce 95% of circulating testosterone (6–7 mg/day) in mens body [3], compared to ovaries in the female body these cells produce 7 to 8 times higher testosterone [4]. A lot of studies were measuring the endogenous level of testosterone. They came to the conclusion that circulating testosterone levels affected amygdala activity among females and males [5, 6], which plays an important role in normal emotional response and psychiatric disorders.

In recent studies it was found that testosterone levels have significant effect on hormone sensitive cancers, type 2 diabetes (T2D), insulin resistance, body fat composition and other related metabolic disease risk factors. Ruth et al. (2020) study found causal positive effects of testosterone levels on lean body mass and number of lifetime sexual partners, which suggests testosterone effects on behavioral patterns [7]. Multiple studies have shown that levels of total and free testosterone is decreasing with age, but the extent of which decline in testosterone is caused by chronic illness, medication use or other factors isn't clearly distinguished from normal decline caused by normal aging [8, 9]. The symptoms of hypogonadism such as tiredness, lack of energy, reduced strength, frailty, loss of libido, decreased sexual performance depression, mood change and are not easily distinguished from symptoms of old age [10]. In this article, we will review the role of testosterone on the onset of type 2 diabetes and other conditions, including mental disorders.

METHODS

This literature review was performed using search criteria on keywords in Our World In Data (OWID) statistics database [11] and the PubMed database. Using keywords 293 articles were selected according to the search criteria. A search of literature on the causes, physiology, and treatment options for type 2 diabetes, depression, anxiety, neurodegenerative disorders including testosterone was carried out. Only English language and full text articles were included in this review. At the end 66 articles were used for this review.

RESULTS

The role of gonadal hormones in affective disorders

In 2017 there were 284 million people with anxiety disorders, making it the most prevalent psychiatric disorder. Around 63% (179 million) of patients with anxiety disorders were female, relative to 105 million males [12]. Current human research has yet to provide a clear understanding of the neural and behavioral mechanisms underlying their etiology, but different prevalence among gender suggests that gonadal hormones are playing an important role in etiology of anxiety and depressive disorders. It is known that the symptoms of premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) occur during fluctuations of gonadal hormones, when estradiol (E2) and progesterone levels are low [13]. Women are more likely to suffer from anxiety during periods of gonadal hormone fluctuations including the premenstrual, postpartum and perimenopausal periods [14]. Data shows that incidence of mood disturbance and anxiety disorders increases as women progress toward menopause, corresponding to a period of falling E2 levels [15, 16]. Recent data shows that higher serum total testosterone and androstenedione in men may relate to an increased risk of anxiety disorders [17] and contradicts findings that testosterone and estradiol exhibit anxiolytic- and antidepressant-like effects in gonadectomized rats [18]. Hypogonadal men have much higher prevalence of anxiety disorders and major depressive disorder, compared to those with normal physiological levels of androgens [19]. Many studies found that testosterone appears to be effective in alleviating anxiety and/or depression in hypogonadal men, but risk factors must also be assessed [16, 20-22].

Major depressive disorder (MDD) is usually a chronic illness with women being two times more likely to be diagnosed with the disorder than man [23, 24]. There are differences in symptoms of MDD between men and women. Women usually have higher MDD related distress and higher severity of symptoms compared to men, also they are more likely to have hyperphagia, hypersomnia, a seasonal effect on mood and anxiety disorder along with their depression as comorbid disease [25, 26]. There is a lot of discussion between testosterone and depression, because testosterone is often described as a neuroactive steroid hormone, which carries weight for mood and appetitive behavior. A lot of studies have investigated the role of testosterone replacement therapy to reduce depressive symptoms and got good results [27, 28]. Giltay found that salivary testosterone levels are lower in female patients with a depressive disorder, generalized anxiety disorder, social phobia, and agoraphobia when compared to female controls but not in men [29]. Bromberger found that higher testosterone levels may contribute to higher depressive symptoms in women. In male patients with depression free testosterone index (FTI) was suggested as the most sensitive biomarker directly showing bioavailable testosterone level [30]. Milman found that higher levels of testosterone was strongly associated with depressive symptoms in Caucasian women [31]. Almeida et al., found that men with depression had significantly lower total and free testosterone concentrations than nondepressed men [32]. It was also observed that men with low testosterone levels more often have depressive symptoms [32, 33], but in some middle-aged and older men conflicting cohort studies there isn't any association between lover testosterone level and depression, only in solitary subtypes of depression. There is another side of testosterone. Some research has shown that the beginning of major depressive disorder in women can be caused by too much testosterone. Also in women excess testosterone can negatively impact their mood [34]. Recent population-based, longitudinal study revealed inverse associations between sex hormones and depressive symptoms and concluded that in general population, androgens and SHBG were not independently associated with depressive symptoms [35]. Since most of the trials that find associations between testosterone and depressive disorder are in very narrow populations or specific age groups, findings

are still contradictory, additional double blind, placebo-controlled, randomized clinical trials are warranted for decisive conclusions.

Gender differences in neurodegenerative disorders

Neurodegenerative disorders like Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS) are characterized by progressive changes of neuronal function in the brain and causes many psychiatric conditions, loss of cognitive and motor functions and the consequent death of patients [36]. There are significant gender differences in incidence of neurodegenerative disorders, twice as many men than women suffer from PD [37] and ALS is more common in men, and in younger age with differences in clinical features [38]. As well as being more likely to be diagnosed with AD, women have been reported as showing greater cognitive deficits than men even in verbal abilities [39]. Circulating levels of androgens and estrogens could have a role in determining gender differences in neurodegenerative diseases. With an increasing number of recent studies confirming testosterones neuroprotective properties [40-42] and although the role of testosterone in the central nervous system (CNS) is still poorly understood. It is important to consider testosterone as a treatment option for neurodegenerative disorders and even to monitor it as a tool for preventative measures. According to Moffat et al., which used a prospective, longitudinal design with follow-up in men since 1958, calculated free testosterone concentrations were lower before diagnosis in men who developed Alzheimer disease. So testosterone may be important for the prevention and treatment of AD [43]. It is important to take into consideration, that effect of testosterone vary depending on age group and levels of testosterone, which suggest that it is possible that there is an optimal levels of testosterone and Sex Hormone Binding Globulin (SHBG), which, if surpessed, is not beneficial but rather has negative effects on cognition [44-46]. Recent studies showed that testosterone administration does improve verbal memory, spatial memory in elderly men [47] overall cognitive functions in men with Alzheimer disease and mild cognitive impairment [48] and as a preventative measure against cognitive decline healthy older men [49].

The role of testosterone on insulin resistance in type 2 diabetes

Many studies show that hypogonadism is associated with insulin resistance in healthy men and can be used to predict T2D in middle aged men, and around one third of men with T2D have low levels of testosterone [50-54]. After studies of hypogonadism in men with T2D have highlighted that low testosterone is an independent risk factor for T2D and testosterone therapy might reduce insulin resistance. Many studies tried to investigate testosterone replacement therapy for hypogonadal men with T2D and investigate its effect on T2D outcomes [55]. Found beneficial effects on insulin resistance, total and LDL-cholesterol, sexual health and body composition in hypogonadal men with T2D [56]. Hackett found that testosterone therapy significantly improved metabolic parameters in men with T2D but only in groups with testosterone deficiency syndrome (TDS) and not in groups with severe TDS. In study by Ng Tang Fui et al., it was found that testosterone treatment significantly reduced the metabolically important visceral fat compared to placebo group [57]. Testosterone therapy also improved glycaemic control, insulin resistance, cholesterol and visceral adiposity and overall cardiovascular risk in hypogonadal men with T2D [58]. Long term studies also proved that testosterone therapy can help improve obesity, glycemic control, blood pressure, and HbA1c [59].

Testosterone as a treatment option in mental disorders

Treatment in patients with depression might require more than 1 treatment step, and more than 30% of patients do not experience sustained symptomatic remission even after 4 treatment steps, and poorer longer-term outcomes were found with participants who required more treatment steps [60], which is why it is important to look into more effective treatment options from first treatment steps. Placebo controlled trial with testosterone therapy in medically healthy adult men with MDD failed to show significant outcomes [61]. Zarrouf et al., found that testosterone showed antidepressant effect in men with hypogonadism or HIV/AIDS and in elderly subpopulations only [16]. Snyder et al., concluded that testosterone therapy showed some benefit with respect to mood and depressive symptoms in males, 65 years or older with low levels of testosterone [62]. Shores et al., confirms effectiveness of testosterone therapy for elderly men with low levels of testosterone for subthreshold depression or late-onset male dysthymia [63, 64]. Recent meta analysis and systematic review done by Walther [65] concludes that testosterone treatment appears to be effective in reducing depressive symptoms in men, particularly when higher-dosage regimens were applied in specific samples. Kleeblatt et al., found that testosterone was clinically effective for depressed hormone-deficient patients who are not responding to antidepressant monotherapy or established augmentation strategies [66]. Randomized study by Ditchel found no effects of testosterone therapy for women with antidepressant-resistant major depression, compared to placebo [67]. Budoff et al., found that testosterone therapy among older men with symptomatic hypogonadism was associated with significantly greater increase in coronary artery noncalcified plaque volume [68].

Augmentation of primary drugs with testosterone or testosterone replacement therapy could be used to treat anxiety, depression, neurodegenerative disorders or type 2 diabetes in some groups that meet narrow criteria, but the results of some studies remain controversial. To ensure safety of treatment augmentation with testosterone replacement therapy extensive long-term controlled clinical trials are still required.

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Pacientų, sergančių depresiniu sutrikimu gydymo antidepresnatais nepageidaujamų reiškinių stebėsena: tarptautinis sutarimas

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SANTRAUKA

Tikslai. Šios rekomendacijos sukurtos siekiant užtikrinti pacientų, sergančių depresiniu sutrikimu (DS) (angl. *major depressive disorder, MDD*) saugumą ir padėti stebėti ir valdyti gydymo antidepresantais nepageidaujamus poveikius. Rekomendacijomis siekiama informuoti gydytojus apie su gydymu susijusias rizikas ir apie metodus, kaip šias rizikas sumažinti.

Metodai. Ekspertai bendraautoriai buvo pakviesti kontaktuojant su pagrindinių suinteresuotųjų šalių tarptautinių profesinių draugijų atstovais, dirbančiais DS gydymo srityje (ASBDD, CANMAT, WFSBP ir ISAD). Rankraštis buvo parengtas ir redaguotas, kol pasiektas galutinis susitarimas.

Rezultatai. Tinkamas rizikos įvertinimas prieš farmakoterapiją ir saugumo stebėjimas farmakoterapijos metu yra esminiai veiksniai, kad sušvelninti nepageidaujamus reiškinius, optimizuoti vaistinio preparato teikiamą naudą, įvertinti ir valdyti nepageidaujamus reiškinius, kai jie atsiranda. Farmakoterapijos rizikos veiksniai skiriasi atsižvelgiant į individualias paciento savybes ir skiriamą gydymo režimą. Rizikos veiksniai turi būti atidžiai įvertinti prieš pradedant farmakoterapiją ir pasirenkamos tinkamos individualios gydymo taktikos. Kai kurie antidepresantai siejami su specifinėmis saugumo problemomis, kurios turi būti išspręstos.

Išvados. Antidepresantų sukeliamų nepageidaujamų reiškinių gydymui būtinas tinkamas vertinimas ir stebėjimas, siekiant pagerinti rizikos ir naudos santykį ir pagerinti klinikinius rezultatus.

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1. ĮVADAS

Antidepresantai yra ketvirta dažniausiai išrašomų medikamentų kategorija Ekonominio bendradarbiavimo ir plėtros organizacijos (angl. *Organisation for Economic Co-operation and Development, OECD*) šalyse, su didėjančia tendencija (Stuart ir kt., 2017). Antidepresantų vartojimas yra susijęs su skirtingo sunkumo ir pasireiškimo dažnio nepageidaujamų reiškinių rizika. Dažniausi šalutiniai reiškiniai yra galvos skausmas, pykinimas, ažitacija, slopinimas, seksualinės disfunkcijos, susilpnėjęs protinis aštrumas ir atmintis, svorio augimas bei metaboliniai sutrikimai (Anderson ir kt. 2012). Retesni ir sunkesni yra kardiologiniai (Dziukas ir Vohra 1991; Jasiak ir Bostwick 2014), ir neurologiniai (įskaitant traukulius) ir kepenų funkcijos nepageidaujami reiškiniai, taip pat ir galimai didesnė suicidiškumo rizika pauglystėje. Nepaisant subjektyvaus diskomforto ir gretutinių ligų, nepageidaujami reiškiniai yra dažniausia antidepresantų nutraukimo priežastis, kuri susijusi su didesne prastų gydymo rezultatų tikimybe (Keitner 2010). Taigi nepageidaujamų reiškinių, susijusių su antidepresantų vartojimu, valdymas yra svarbus dalykas tiek pacientų saugumui ir tiek realaus gydymo veiksmingunmo padidinimui. Taigi nepageidaujamų reiškinių, susijusių su antidepresantų vartojimu, valdymas yra svarbus dalykas pacientų saugumui ir realaus pasaulio efektyvumo didinimui. Šiame kontekste svarbu atkreipti dėmesį į tai, kad negydomas psichikos sutrikimas kelia daugybę rizikų ir neigiamų pasekmių, o rizika, kad liga yra negydoma, dažnai yra nepripažįstama (Berk ir Parker 2009).

Tarptautinė Pasaulinės biologinės psichiatrijos draugijų federacijos (WFSBP) darbo grupė yra parengusi vienpolių depresinių sutrikimų biologinio gydymo praktines rekomendacijas (Bauer ir kt. 2002a; Bauerir kt.2002b; Bauer ir kt.2007; Bauer ir kt. 2013; Bauerir kt., 2015). Kanados nuotaikos ir nerimo gydymo tinklas (CANMAT) parengė pacientų, sergančių sunkia depresija (MDD), gydymo klinikines gaires, o šiose rekomendacijose pateikiamos pacientų saugumo rekomendacijos (Kennedy ir kt.2016; Lam ir kt., 2016). Neseniai buvo parengtos vaistų nuo depresiniossutrikimo (DS, angl. *Major depressive disorder, MDD*) rekomendacijos, kurios dokumentuoja Floridos ekspertų grupės sutarimo rekomendacijas ir apima saugos rekomendacijas (McIntyre ir kt., 2017). Australijos specialistams taip pat buvo paskelbtos regioninės antidepresantų vartojimo gairės (Dodd ir kt., 2011). Manome, kad reikia naujų sutarimo rekomendacijų, kurios konkrečiai spręstų antidepresantų gydymo saugumą, turėtų platesnį tarptautinį sutarimą ir atnaujintų ankstesnes gaires. Šios rekomendacijos atspindi ekspertų sutarimą dėl pacientų vertinimo ir stebėjimo prieš pradedant ir gydant DS. Šios rekomendacijos pateikiamos patogiu naudoti formatu kaip praktinis vadovas gydytojams. Visi bendraautoriai patvirtino galutinę rekomendacijų versiją, kurią taip pat patvirtino WFSBP, CANMAT, Australazijos bipoliarinių depresijos sutrikimų draugija (ASBDD) ir Tarptautinė afektinių sutrikimų draugija (ISAD).

2. METODAS

Tyrėjai, kurie yra ASBDD ir CANMAT nariai, paskatino ketinimą paskelbti naujausias tarptautines bendro sutarimo rekomendacijas dėl antidepresantų vartojimo gydant DS, abi organizacijos oficialiai remia šį projektą. Buvo kreiptasi į WFSBP ir ISAD ir buvo paskirti bendraautoriai iš visų dalyvaujančių organizacijų. Autoriai buvo atrenkami atsižvelgiant į jų patirtį, patirtį, narystę dalyvaujančioje visuomenėje ir norą dalyvauti. Šių bendro pobūdžio rekomendacijų taikymo sritis apsiribojo vaistų, kurie yra pagrindinė antidepresantų terapija DS, saugos klausimais.

Augmentaciniai medikamentai, ne pagal indikacijas skiriami vaistai ir vaistai, pirmiausia naudojami kitoms indikacijoms, nepatenka į šią vertinimo sritį. Nuo 2015 m. lapkričio mėn. iki 2016 m. sausio mėn. daugybė išsamių kompiuterizuotų recenzuojamos literatūros paieškų buvo atliekamos neribojant datos. Buvo ieškoma „Pubmed“, OVID, „Medline“ ir atitinkamų leidinių nuorodų sąrašų. Duomenys kelis kartus buvo atliekami atskirų bendraautorių vėliau iki 2016 m. Lapkričio mėn. Buvo parengtos ir išplatintos rekomendacijos redagavimui ir bendraautorių atsiliepimams kartoti, kol visi bendraautoriai patvirtins galutinę versiją. Buvo paprašyta ASBDD, CANMAT, WFSBP ir ISAD pritarimo, kad šios susitarimo rekomendacijos būtų susietos su šiomis draugijomis. Rekomendacijos išdėstytos skyriuose; vertinimas (3 skyrius), stebėjimas (4 skyrius), specialios grupės (5 skyrius), nepageidaujamų reiškinių valdymas (6 skyrius) ir perdozavimo valdymas (7 skyrius). Kai kurie saugumo klausimai kyla daugiau nei viename skyriuje (pvz., Kepenų funkcija) ir buvo stengiamasi išvengti pasikartojimo. Gydymo antidepresantais saugumo stebėjimo rekomendacijų santrauka pateikta 1 lentelėje.

3. BENDROS REKOMENDACIJOS DĖL ANTIDEPRESANTŲ VARTOJIMO

3.1. Įvertinimas, ar reikia pradėti ar tęsti DS gydymą

Kiekvienam naujam pacientui, kenčiančiam nuo DS, sprendimas skirti antidepresantą – ar ne – turi būti įvertintas bendradarbiavimo ir terapinio aljanso požiūriu (Berk ir kt., 2004). Gydymą reikia pradėti arba tęsti, jei pacientas sutinka su gydymo planu ir režimu, pripažįsta jo riziką ir naudą, o gydantis gydytojas mano, kad gydymo nauda yra didesnė už riziką. Kruopštus vertinimas turėtų būti atliekamas individualiai. Prieš nustatant diagnozę ar priimant sprendimus dėl gydymo, turėtų būti atliktas diagnostinis darbas, siekiant užtikrinti, kad būtų sprendžiamos potencialiai svarbios ar komplikuojančios medicininės ar psichinės būklės. Tuomet sprendimą dėl gydymo ar negydymo reikia aptarti su pacientu, taip pat aptarti visas gydymo galimybes, įskaitant psichosocialinį intervenciją, jei ji tinkama. Šios apžvalgos 3.3 skirsnyje pateikti vertinimai gali būti naudingi diagnostikos aiškumui pagerinti.

3.2. Gydymo pasirinkimas

Gydymas pasirenkamas atsižvelgiant į daugybę pašalinių veikėjų, įskaitant atskirų antidepresantų veiksmingumą ir toleravimą, praeities atsaką ir toleranciją, asmens klinikinių simptomų pobūdį, asmenines nuostatas ir išlaidas.

Antidepresantų deriniai, padidinimo strategijos ir kitos vaistų parinktys bei somatinė terapija paprastai yra rezervuota tiems, kurie nereagavo į antidepresantų monoterapiją (Dodd ir kt., 2005) ir nepatenka į šių rekomendacijų taikymo sritį. Šiose rekomendacijose neatsižvelgiama į atskirų gydymo būdų saugumo ir toleravimo palyginimą. Atvirkščiai, jomis

1 lentelė. **Antidepresantų saugumo monitoringo rekomendacijų santrauka**

	Rekomendacijos
Pradiniai įvertinimai	Labai rekomenduojama
	• Diagnostika / diferencinė diagnozė, įskaitant organinių depresijos priežasčių įvertinimą
	• Asmeninė ir šeimos istorija, apimanti ankstesnį antidepresantų vartojimą
	• Fizinė sveikata, įskaitant kūno masės indeksą ir (jei reikia) liemens apimtį; metabolinis sindromas; seksualinė sveikata / disfunkcija; hipertenzija; alkoholis, tabako ir psichoaktyvių medžiagų vartojimas bei priklausomybė
	Taip pat reikia atsižvelgti
	• Nėštumo testas
	• Kepenų funkcijos tyrimas (reikalingas agomelatinui)
	Gali būti svarstoma
	• Elektrokardiograma esant širdies ir kraujagyslių ligoms
	• Kaulų tankio nuskaitymas, ypač kai yra osteoporozės rizikos veiksnių; Elektrolitai, ypač. vyresnio amžiaus pacientams
Įvertinimai gydymo metu	Patikrinkite, ar nėra pokyčių, palyginti su pradiniu vertinimu
	• Svoris ir (jei reikia) liemens apimtis
	• Seksualinė disfunkcija
	Patikrinkite, ar nėra neigiamo gydymo poveikio
	• Savižudiškos mintys, ypač jaunų žmonių
	• Padidėjęs transaminazių kiekis serume (reikalingas agomelatinui)
	Hiponatremija, ypač vyresnio amžiaus žmonėms
	• Hipertenzija; ortostatinė hipotenzija
Ypatingos populiacijos	Ypatingas dėmesys turi būti skiriamas vaikams, pagyvenusiems žmonėms, reprodukcinio amžiaus moterims ir žmonėms, turintiems psichikos ir fizinių sutrikimų

siekiama pateikti rekomendacijas dėl pacientų ir su vaistais susijusių veiksnių, į kuriuos reikėtų atsižvelgti vertinant gydymo pasirinkimo saugumą ir toleravimą.

3.3. Prieš gydymą atliekamas įvertinimas

Pradiniame vertinime pateikiama informacija apie klinikinę būklę prieš pradedant gydymą, todėl turėtų būti nustatyti pradiniai parametrai, skirti stebėti saugumą ir toleravimą gydymo metu. Duomenys apie sutrikimo pobūdį ir eigą, išsamią klinikinę istoriją, diferencinę diagnozę, medicinines ir psichines gretutines ligas, praeities istoriją ir šeimos atsaką į gydymą / nereagavimą ir toleravimą yra būtini norint pasirinkti gydymo būdą, kuris taip pat turi būti pritaikytas asmeninius pageidavimus, taip pat kultūrinius ir aplinkos veiksnius.

3.3.1. Skalės ir įvertinimas prieš paciento apklausą arba jos metu

Savarankiškai įvertinti klausimynai gali būti naudojami laukiamajame ar internete, kad padėtų rinkti tokią informaciją kaip medicininė ir šeimos istorija. Naudojant simptomų skales, pacientų ir šeimos anketas bei atrankos įrankius gali būti lengviau rinkti duomenis ir tai gali būti praktiška daugelyje praktikos sąlygų. Nėra rekomenduojamų specialių psichinės sveikatos priemonių; tačiau kai kurios sveikatos tarnybos gali įpareigoti naudoti tam tikrus klausimynus ir skales. Taip pat yra išsamių struktūrinių diagnostinių interviu skalių, leidžiančių nustatyti gretutinius psichikos sutrikimus, nors jie paprastai užima daug laiko ir paprastai yra skirti tik tyrimų tikslams. Komorbidinius medžiagų vartojimo sutrikimus reikia gydyti arba pacientus nukreipti specialistams, atsižvelgiant į vietinius protokolus. Kiti vaistai, kuriuos šiuo metu vartoja pacientas, turėtų būti dokumentuoti ir įvertinta vaistų sąveikos rizika

3.3.2. Laboratoriniai tyrimai

Daugumoje nacionalinių ir tarptautinių rekomendacijų nagrinėjami laboratoriniai tyrimai prieš gydymą antidepresantais ir jų metu.

Jų įtraukimas į šias dabartines tarptautines rekomendacijas yra ginčytinas, nes tyrimai gali būti nereikalingi, nebūtinai ekonomiški ir gali be reikalo padidinti gydymo išlaidas. Kai kuriuos testus įpareigoja atlikti vaistų priežiūros institucijos tose valstybėse ar regionuose, kuriuose šios priežiūros institucijos yra veikiančios ir kompetentingos. Šiuo metu vieninteliai pradiniai laboratoriniai tyrimai, kuriuos užsakė sveikatos priežiūros agentūros, yra kepenų funkcijos tyrimai prieš pradedant gydymą agomelatinu ir nefazodonu, jo metu ir po jo. Reglamentus dėl agomelatino inicijavo Europos vaistų agentūra (EMA), įskaitant tai, kad to pradėti negalima arba gydymas turi būti nutrauktas, jei serumo transaminazių koncentracija viršija tris kartus viršutinę normos ribą (Europos vaistų agentūra, 2008). Patentinis nefazodonas buvo nutrauktas 2003 m. dėl nepageidaujamų kepenų poveikių, nors kai kuriose rinkose vis dar yra kai kurių generinių vaistų. Kitur kitos reguliavimo institucijos patvirtino farmacijos kompanijų pateiktą informaciją apie produktą, įskaitant EMA bandymų reikalavimus.

Dėl įprastinio pradinių laboratorinių tyrimų naudojimo yra skirtingos nuomonės, atspindinčios įrodymų ribotumą

ir skirtingus atskirų šalių standartus. Pavyzdžiui, CANMAT rekomendacijose nepatartina atlikti įprastų laboratorinių tyrimų, įskaitant terapinį vaistų stebėjimą ir genetines bei CYP450 analizes, ir rekomenduojama atlikti tokius tyrimus tik tada, kai yra klinikinių indikacijų. Priešingai, kai kurios šalys turi gaires ir taisykles, kuriose kai kurie tyrimai, pavyzdžiui, agomelatinu gydytų pacientų kepenų funkcijos tyrimai, yra privalomi. Taigi šiose tarptautinėse konsensuso rekomendacijose aprašoma, kokie testai galimi, nepateikiant rekomendacijų dėl konkretaus testo naudojimo. Vykdomos tolesnės mokslinių tyrimų pastangos, o rekomendacijos gali pasikeisti, kai atsiras naujų duomenų. Klinikinėje praktikoje dauguma gydytojų paprastai neskiria laboratorinių tyrimų prieš ir po gydymo antidepresantais. Kita vertus, laboratoriniai tyrimai gali būti naudingi norint nustatyti pradinius matavimus prieš pradedant gydymą, nustatyti rizikos veiksnius ir neįtraukti fizinių ligų, sukeliančių depresijos simptomus. Sprendimą prašyti bandymų gali turėti įtakos vietiniai reglamentai, prieinamumas ir bandymų kaina. Sprendimai taip pat gali būti priimami kiekvienu atveju atskirai, atsižvelgiant į riziką ir asmeninius pageidavimus.

3.3.2.1. Testai, skirti atmesti kitas medicinines diagnozes, atliekant DS diferencinę diagnostiką.

Pilnas kraujo tyrimas: Pilnas kraujo tyrimas yra naudingas norint įvertinti, ar depresijos simptomai yra susiję su anemija ir jos priežastimis, įskaitant B12 ar folatų trūkumą, ar sisteminį uždegimą, nustatytą padidėjus baltųjų kraujo kūnelių skaičiui.

Skydliaukės funkcija: Hipotirozė (ir kiek mažiau hipertirozė) gali būti siejama su tokiais simptomais kaip emocinis nestabilumas, kognityviniai sutrikimai, nuovargis ir mieguistumas, kurie gali būti neteisingai diagnozuoti kaip DS (Bauer ir kt., 2008). Daugeliu atvejų skydliaukę stimuliuojančio hormono (TSH) lygis yra laikomas tinkamu ekranu subklinikinei ar prasidedančiai hipotirozei nustatyti. Du dideli ambulatorinių pacientų, sergančių depresija, kohortos tyrimai (Iosifescu ir kt., 2001; ir Fava ir kt., 1995) parodė, kad hipotirozė ir hipertirozė yra nedažni, nė viename tyrime nėra klinikinių atvejų ir kad yra subtilių skydliaukės funkcijos sutrikimų. neatrodo, kad turėtų įtakos gydymo rezultatams (Fava ir kt., 1995; Iosifescu ir kt., 2001). Jei pacientams, sergantiems depresija, nustatoma nenormali skydliaukės funkcija, reikia normalizuoti TSH ir skydliaukės hormonų kiekį (T3 ir T4). Jei gydytojas nėra susipažinęs su skydliaukės hormonų kiekio koregavimu, pacientus reikia nukreipti pas endokrinologą ar internistą. Depresijos simptomai gali išnykti, kai pakoreguojamas nenormalus skydliaukės hormono kiekis. Pacientų pogrupyje gali reikėti papildomai gydyti depresijos simptomus antidepresantais (bet kurios klasės). Reikėtų pažymėti, kad skydliaukės disfunkcija buvo susijusi su neatsakymu į gydymą, net jei tai buvo koreguota (Berlin ir kt., 1999; Dodd ir Berk 2004).

Piktnaudžiavimo alkoholiu ir narkotikais ir priklausomybės patikra: Piktnaudžiavimas alkoholiu ir narkotikais bei priklausomybė yra dažnas komorbidiškuamas su DS. Jų nustatymas yra svarbus ne tik klinikiniam gydymui, bet ir farmakoterapijos saugumo sumetimams. Diagnostiką gali supainioti netaskleistas medžiagų vartojimas, apsinuodijimas ar medžiagų pašalinimas, ypač psichostimuliatorių vartojimas, kuris imituoja nuotaikos sutrikimo simptomus (Barr ir kt. 2002) Farmakodinaminė ir farmakokinetinė vaistų sąveika su alkoholiu, tabaku ir neteisėtomis medžiagomis yra didelė rizika (Dodd ir kt., 2011). Tikslinga reguliariai teirautis apie naudojimą, net jei neatitinka priklausomybės ar piktnaudžiavimo kriterijų. Su alkoholiu (Menkes ir Herxheimer2014) ir tabaku (Nemeroff ir kt. 1996) susijusi rizika yra gerai žinoma. Mažiau žinoma apie antidepresantų ir neteisėtų narkotikų sąveiką, kai atvejų pranešimai parodė potencialiai rimtą riziką (Silins ir kt., 2007). Kraujo, seilių ar šlapimo patikra, siekiant nustatyti medžiagas, ir alkoholio ar iškvėpto anglies monoksideko kvėpavimo tyrimai gali aptikti tik medžiagas, esančias tyrimo metu. Informacija, surinkta iš šeimos, draugų ir kitų sveikatos priežiūros specialistų, gali būti patikimesnė ir padėti suprasti žmogaus narkotines medžiagas ir alkoholį. Kaip ir vartojant neteisėtas medžiagas, kai kurie receptiniai vaistai gali sukelti ar sustiprinti depresijos simptomus ir sukelti vaistų sąveiką (Dodd ir kt., 2011). Naudojant savęs ataskaitų skales, įskaitant Narkotikų piktnaudžiavimo atrankos testą (Gavin ir kt., 1989) ir Mičigano alkoholio atrankos testą (Selzer1971), gali būti privalumų, palyginti su laboratoriniais tyrimais, pavyzdžiui, mažesnės išlaidos, didesnis jautrumas ir nauda terapiniam aljansui.

Infekcinių ligų patikra: Infekcinės ligos kartais gali sukelti simptomus, kurie sutampa su DS, įskaitant somatinius simptomus, nuovargį, negalavimo skausmus ir skausmą (Maes 2009). Šie simptomai gali išlikti, kai ūminė infekcija išnyks (Nolanir kt., 2012). Virusinės ir kitos infekcijos gali būti tikrinamos naudojant kraujo mėginius. Infekcijos simptomai, tokie kaip nuovargis ir anhedonija, gali sutapti su depresijos simptomais. Kai kurios virusinės infekcijos taip pat siejamos su didesniu DS dažniu, įskaitant žmogaus imunodeficito virusą (ŽIV) (Shacham ir kt. 2009), hepatitą C (Bailey ir kt., 2009), Vakarų Nilo virusą (Murray ir kt., 2007) ir Epstein-Barr virusas (Milleris ir kt., 1986; Milleris ir kt., 2005). Eritrocitų nusėdimo greitis ir C reaktyvaus baltymo lygis gali būti informatyvus įtarus infekciją, nors šie tyrimai yra gana nespecifiniai. Pranešama, kad depresijos simptomai yra dažniausiai pasitaikantis interferono gydymo hepatitu C šalutinis poveikis, o išankstinis gydymas SSRI gali užkirsti kelią depresijos simptomams, susijusiems su gydymu interferonu (Lucaciu ir Dumitrascu 2015).

24 valandų laisvas kortizolio šlapimo tyrimas: tai gali nustatyti hiper- ir hipokortizolemiją, kurios kiekviena gali pasireikšti su depresijos simptomais (Wolkowitz ir kt., 2009). Depresijos simptomai, susiję su Kušingo sindromu, gali išnykti gydant endokrininį sutrikimą (Wolkowitz ir kt., 2009). Endokrininiai sutrikimai išsamiau aptariami šios apžvalgos 5.3.4 skyriuje.

Neurovizualinis tyrimas ir kognityviniai neuropsichologiniai tyrimai: Vėlyvos pradžios DS atsiradimui magnetinio rezonanso tyrimas (MRT) gali būti naudingas, įvertinant ar smulkiųjų kraujagyslių liga yra pagrindinė priežastis (O'Brien ir kt., 1998). Kognityviniai neuropsichologiniai tyrimai gali nustatyti kognityvinius sutrikimus. DS siejamas su daugeliu vykdomosios funkcijos ir atminties sutrikimų (Wright ir Persad 2007; Snyder 2013; Keefe ir kt., 2014). MRT ir kognityviniai neuropsichologiniai tyrimai taip pat gali būti naudinga bazinė priemonė būsimiems vertinimams, ypač todėl, kad vėlyvosios pradžios DS buvo

nustatytas kaip demencijos rizikos veiksnys (Kohler ir kt., 2015).

3.3.2.2. Tyrimai, reikalingi pradiniam funkcionavimui įvertinti, kuriems įtakos gali turėti antidepresantų vartojimas.

Kūno svoris: DS ir gydymas antidepresantais yra susiję su kūno svorio pokyčiais. Kūno svorio pokyčiai dažnai kelia susirūpinimą pacientams, gydomiems antidepresantais, bei yra susiję su daugeliu komorbidinių somatinių ligų (Fava, 2000). Padidėjęs kūno svoris gali sąlygoti metabolinio sindromo vystymąsi (Heiskanen, 2015). Kūno svoris ir liemens apimtis turi būti matuojami ir registruojami prieš gydymo antidepresantais pradžią. Ne vieninga, bet daugumos šio sutarimo autorių nuomone, metabolinio sindromo rodmenys – lipidų koncentracija, arterinis kraujo spaudimas ir glikemija turi būti matuojami tik esant indikacijoms.

Seksualinė sveikata: gydymo metu atsiradusi (angl. *treatment-emergent*) seksualinė disfunkcija yra dažnas šalutinis gydymo antidepresantais poveikis. Tyrimų duomenimis 27–65% moterų ir 26–57% vyrų gydymo antidepresantais pradžioje pasireiškia arba buvusių seksualinių sutrikimų pablogėjimas arba nauji gydymo metu atsiradę seksualinės funkcijos sutrikimai (Baldwin ir kt., 2013). Vis dėl to, šis šalutinis poveikis ne retai pasireiškia anamnezėje esant gydymo nereikalaujantiems seksualinės funkcijos sutrikimams. Remiantis tyrimo duomenimis, 26% tiriamųjų, nesergančių psichikos liga, 45% antidepresantais negydomų depresija sergančių tiriamųjų ir 63% antidepresantais gydomų tiriamųjų, turėjo tam tikrų seksualinės funkcijos sutrikimų (Angst, 1998). Seksualinei sveikatai įvertinti turėtų būti naudojamos validuotos skalės, tokios kaip: Arizonos seksualinių patirčių skalė (angl. *Arizona Sexual Experiences Scale, ASEX*), Lytinės funkcijos indeksas (angl. *Sexual Functioning Inventory, SFI*), Seksualinio funkcionavimo pokyčių klausimynas (angl. *Changes in Sexual Functioning Questionnaire, CSFQ*), Su psichotropiniais medikamentais susijusios seksualinės disfunkcijos klausimynas (angl., *the Psychotropic-Related Sexual Dysfunction Questionnaire, PRSexDQ-SALSEX*) ir Lytinio poveikio skalė (angl. *the Sex Effects Scale*).

Kardiologinis saugumas: Arterinis kraujo spaudimas (AKS) ir širdies susitraukimų dažnis (ŠSD) taip pat turi būti patikrinti, dėl kai kurių medikamentų poveikio į AKS; kardiovaskulinės ligos yra rizikos faktorius kardiovaskuliniams šalutiniams reiškiniams pasireikšti (Spindelegger ir kt., 2014).

Nėštumo testas: ar pacientė nėra nėščia – turėtų būti patikslinta visoms reprodukcinio amžiaus moterims prieš skiriant gydymą antidepresantais, o esant neaiškumui, gali būti atliekamas nėštumo testas. Nėštumas susijęs su kai kurių antidepresantų ir jų metabolitų poveikiu vaisiui, taigi ir teratogeniškumu, bei kai kurių medikamentų farmakokinetikos pokyčiais. Dėl to DS gydymas medikamentais turi priklausyti ir nuo pacientės reprodukcinės būklės (Deligiannidis ir kt., 2014).

Kepenų funkcijos tyrimai (KFT): Vyresnio amžiaus pacientai, pacientai turintys gretutinių ligų ar vartojantys keletą medikamentų yra laikomi didelės rizikos grupėmis turėti pakitusią kepenų funkciją. Hepatitas C yra siejamas su depresijos simptomais, nepriklausomai nuo gydymo interferonu-α ir piktnaudžiavimo psichoaktyviomis medžiagomis (Carta ir kt., 2007). Transaminazių koncentracijos kraujo serume ir kitų kepenų pažaidos rodiklių ištyrimas yra rekomenduojamas esant kepenų funkcijos sutrikimo įtarimui pagal klinikinius požymius, tokius kaip komorbidinis piktnaudžiavimas alkoholiu. Kuomet pakitę KFT nustatomi prieš gydymo antidepresantais pradžią, turi būti nustatoma šių pakitimų priežastis ir jei kepenų pažaidos lygis yra kliniškai reikšmingas, gydymas antidepresantais turi būti atidedamas iki sutrikusios kepenų funkcijos korekcijos. Jei pradiniai KFT yra ne normos ribose ir esant klinikinėms indikacijoms (pvz.: kepenų fermentų padidėjimas du kartus virš normos), gydymui turi būti pasirenkami antidepresantai, siejami su mažesne rizika sukelti kepenų funkcijos sutrikimą. Tokiais atvejais, įvertinus naudos ir žalos santykį, gali būti pradedamas gydymas antidepresantais, gydymo eigoje monitoruojant kepenų funkciją. Įprastai, šie kraujo tyrimai atliekami kartą per metus, nebent yra priežasčių juos kartoti dažniau. Pacientų, su antidepresantų sukelta kepenų pažaida, gydymo rekomendacijos yra aprašytos 6 skyriuje. Pacientų, sergančių kepenų liga, gydymas antidepresantais aptartas 5.3.1 skyriuje ir kepenų funkcijos sutrikimas kaip šalutinis gydymo antidepresantais poveikis aptartas 6.1 skyriuje.

Farmakogenetinis tyrimas: šis tyrimas prieinamas vis didesniam genų, susijusių su farmakokinetiniais ir farmakodinaminiais pokyčiais, skaičiui (Singh ir Bousman, 2017). CYP2D6 ir CYP2C19 fermentų sistemų genų variantų tyrimas nustatant metabolizmo tipą yra labiausiai įrodymais pagrįstas farmakogenetikos tyrimas, reikšmingas gydant antidepresantais (Muller ir kt., 2013). Yra duomenų, rodančių galimą šio tyrimo naudą tam tikrais atvejais (Brennan ir kt., 2015), bet jų nepakanka, naudojimą kasdienėje klinikinėje praktikoje, pagrįsti. Tarptautinė Psichiatrinės Genetikos asociacija (angl. *The International Society for Psychiatric Genetics*) nerekomenduoja genetinio tyrimo pacientams, vartojantiems antidepresantus (angl. *International Society of Psychiatric Genetics,* 2016). Reikalinga daugiau įrodymų, norint patvirtinti šio tyrimo naudą klinikinėje praktikoje, bei jo kainos ir naudos santykį (Bousman ir Hopwood, 2016).

Elektrokardiograma (EKG): Šis tyrimas gali būti naudojamas širdies laidumo sutrikimų nustatymui bei pradinės širdies funkcijos vertinimui prieš pradedant gydymą antidepresantais. Pranešta apie EKG pakitimus vartojant triciklius antidepresantus (TCA), SSRI, SNRI, mirtazapiną ir bupropioną, ypatingai vyresnio amžiaus pacientams bei esant didelėms medikamentų dozėms (Goldberg ir Ernst, 2012). Pradinės EKG atlikimas yra rekomenduojamas pacientams, sergantiems kardiovaskulinėmis ligomis (Dodd ir kt., 2011).

Kaulų tankio matavimas: epidemiologinių tyrimų duomenys rodo ryšį tarp serotoninerginio poveikio antidepresantų vartojimo ir kaulų mineralinio tankio pokyčių. Šie duomenys siejami su įrodymais jog serotoninerginio poveikio medikamentai turi įtakos osteoblastų ir osteoklastų vystymuisi ir kaulo formavimuisi (Williams ir kt., 2008; Hodge ir kt., 2013), nors klinikinė šių duomenų reikšmė dar tiriama. Pradiniai kaulo tankio matavimo rodmenys gali būti naudingi pacientams turintiems didelę osteoporozės riziką, norint įvertinti kaulų tankio pokyčius po ilgalaikio medikamentų vartojimo. Reikia pažymėti, jog ne tik antidepresantų

vartojimas yra rizikos faktorius osteoporozei išsivystyti bet ir DS (Fernandes ir kt., 2016). Taip pat, daugelis žinomų DS rizikos faktorių didina ir osteoporozės riziką, įskaitant nepakankamą fizinį aktyvumą, nepilnavertę dietą ir rūkymą. Kulno ultragarso, kaip kaulų kokybės mato, tyrimas buvo pasiūlytas kaip atrankos tyrimas mažesnės rizikos pacientams, nesusijęs su jonizuojančiosios spinduliuotės rizika, nors šio tyrimo kaip ir dvigubos energijos rentgeno absorbciometrijos tyrimo naudojimo klinikinėje praktikoje naudą reikia detaliau ištirti (Williams ir kt., 2013; Rauma ir kt., 2015). Kaulų sveikata detaliau aptarta 5.3.2 skyriuje.

4. STEBĖJIMAS GYDYMO ANTIDEPRESANTAIS LAIKOTARPIU

Svorio ir, esant galimybei, liemens apimties pokyčiai nuo gydymo pradžios turėtų būti atžymėti konsultacijų metu. Metabolinio sindromo rodikliai turi būti stebimi esant indikacijoms. Šalutiniai reiškiniai seksualinei funkcijai taip pat turi būti vertinami konsultacijų metu ir esant indikacijoms vertinami validuotomis skalėmis.

Gydymo antidepresantais pradžia (1–2 gydymo mėnesiai) siejama su galima didesne suicidinių minčių ir suicidinio elgesio rizika 18–24 m. amžiaus pacientų grupėje (Hammad ir kt., 2006). Šie tyrimų duomenys buvo įtraukti į JAV maisto ir vaistų administracijos (angl. *U.S. Food ir Drug Administration, FDA*) „Įspėjimų sąrašą“, ko pasekoje stebėtas sumažėjęs SSRI grupės antidepresantų skyrimas ir išdavoje-padidėjęs suicidinių atvejų skaičius. (Gibbons ir kt., 2007; Friedman, 2014). Naujausių tyrimų duomenys nerodo aiškios padidėjusios savižudybės rizikos jauniems pacientams, gydomiems antidepresantais (Gibbons ir kt., 2012). Vis dėl to, nauja 12 klinikinių tyrimų meta-analizė, parodė didesnį suicidinių įvykių pasireiškimą antidepresantais gydomų tiriamųjų grupėje lyginant su gydomų placebu tiriamųjų grupe (visose amžiaus grupėse) (Baldessarini ir kt., 2017). Norint pilnai įvertinti riziką, reikalinga atlikti daugiau tyrimų. Nors šiuo metu vertinama, jog gydymo antidepresantais nauda nusveria savižudybės riziką, būtinas jaunų pacientų savižudybės rizikos stebėjimas ūmioje depresinio susirgimo fazėje ir bent 1 mėnesį pasiekus remisiją.

Kraujo tyrimai gali būti atliekami gydymo eigoje. KFT yra būtini gydant agomelatinu tam tikrose šalyse, remiantis už vaistų saugumą atsakingų institucijų nurodymais. Šie tyrimai yra būtini prieš pradedant gydymą, po 3, 6, 12 ir 24 savaičių nuo gydymo pradžios, kai yra didinama dozė ar atsiranda klinikinių indikacijų (Servier Laboratories, 2014). Šio tyrimų tvarkaraščio gali llaikytis ir kiti gydytojai, nepriklausantys šių institucijų pavaldumui, ar naudoti jė tvarkaraštį ir skiriant kitus antidepresantus. Gydymas agomelatinu ir nefazodonu turi būti iškart nutraukiamas jei serumo transaminazių aktyvumas daugiau kaip 3 kartus viršija viršutinę normos ribą arba pacientui atsirado galimos kepenų pažaidos simptomų ar požymių. Duomenų apie pakartotinį agomelatino skyrimo saugumą, normalizavusis transaminazių aktyvumui, nėra, todėl pakartotinis skyrimas nerekomenduojamas.

Širdies funkcijos stebėjimas įskaitant ir AKS matavimą rekomenduojamas jei monoaminooksidazės inhibitoriai (MAOI), TCA ar didelės dozės citalopramo (Castro ir kt., 2013) yra skiriami pacientams turintiems kardiovaskulinių ligų rizikos veiksnių, įskaitant metabolinį sindromą, rūkantiems pacientams ar pacientams, turintiems kardiovaskulinių ligų šeiminę anamnezę. Antidepresantų skyrimas sergant kardiovaskulinėmis ligomis aptartas 5.3.3 skyriuje. Kardiologinis saugumas esant perdozavimui aptartas 7 skyriuje. AKS pokyčiai gydymo pradžioje yra susiję su tam tikrais antidepresantais. Hipertenzija yra siejama su gydymo venlafaksinu ir desvenlafaksinu (Thase ir kt., 2015), ortostatinė hipotenzija – su gydymo fenelzinu, tranilciprominu ir TCA pradžia (Moller ir kt., 1983).

4.1 Kitų rizikos grupių pacientų stebėjimas

Rizikos grupėse esančius pacientus reikia stebėti dėl hiponatremijos rizikos. SSRI ir SNRI grupės preparatai, ypač sertralinas ir escitalopramas yra siejami su hiponatremijos rizika, kuri taip pat dokumentuota ir kitiems vaistams, pavyzdžiui, mirtazapinui (Jung ir kt., 2011). Hiponatremijos rizika yra reikšminga vyresnio amžiaus pacientams ir didesnė moterims (Giorlando ir kt., 2013). SSRI ir SNRI siejami su didesne hiponatremijos rizika, lyginant su kitais antidepresantais (Giorlando ir kt., 2013). Yra duomenų, leidžiančių manyti, kad hiponatremija nepriklauso nuo dozės (Giorlando ir kt., 2013). Prieš pradedant gydymą SSRI ar SNRI senyviems pacientams reikia atlikti elektrolitų ištyrimą. Šiems pacientams elektrolitų ištyrimą reikia atlikti prieš gydymą ir po pirmųjų 3–5 savaičių nuo gydymo antidepresantais pradžios arba įtariant hiponatremijos simptomus (pykinimą, vėmimą, galvos skausmą, sumišimą, nuovargį, raumenų silpnumą).

Antidepresantų terapinis medikamento stebėjimas (TMS) (angl. therapeutic drug monitoring, TDM) gali būti naudojamas medikamento ir metabolitų koncentracijoms kūno skysčiuose nustatyti (Hiemke, 2008). Nors antidepresantų TMS gali būti naudingas gydant TCA, jo naudojimas saugumo vertinimui yra ribotas. Jei yra priežasčių įtarti neįprastą vaisto koncentraciją, vietoje TMS, galima apsvarstyti vaisto ir metabolito koncentracijos matavimą viename biologinio skysčio mėginyje. TMS gali būti brangus, nepasiekiamas arba nepakankamos kokybės. Jei TMS rodo per didelę arba mažą antidepresanto koncentraciją plazmoje, gali prireikti papildomų tyrimų, norint nustatyti priežastis. Medikamento nevartojimas yra dažniausia mažos antidepresantų koncentracijos plazmoje priežastis, o TMS gali parodyti neteisingus rezultatus tiems pacientams kurie medikamentus vartoja tik kelias dienas prieš atliekamą vaisto koncentracijos tyrimą.

Antidepresantų vartojimas taip pat siejamas ir su retais nepageidaujamais reiškiniais, tokiais kaip kraujo diskrazijos (Levin ir DeVane, 1992). Šie neįprasti šalutiniai reiškiniai yra pernelyg reti, kad būtų pateisinamas susijusių tyrimų reguliarius atlikimas; vis dėl to, gydantys gydytojai turėtų būti budrūs dėl jų simptomų. Jie nėra susiję su antidepresanto doze.

5. SPECIALIOS POPULIACIJOS

5.1 Vaikų populiacija

Antidepresantų vartojimas vaikų populiacijoje yra prieštaringas dėl susirūpinimo saugumu, toleravimu ir veiksmingumu, taip pat ir dėl įrodymų iš aukštos kokybės klinikinių tyrimų trūkumo (Jureidini ir kt., 2004). Vaikams turėtų būti skiriamos amžių ir kūno svorį atitinkančios antidepresantų dozės bei geresnes toleravimo savybes turintys antidepresantai turėtų būti pirmo pasirinkimo. Antidepresantų

vartojimas vaikų populiacijoje yra prieštaringas, dėl to dažniausiai teikiama pirmenybė psichologinei terapijai/psichologinėms intervencijoms. JAV FDA paskelbtas „Įspėjimas“ dėl padidėjusios suicidinių minčių ir ketinimų rizikos vaikams ir paaugliams vartojantiems antidepresantus išlieka.

5.2. Nėštumas ir žindymas

Visi antidepresantai gali pereiti per placentą ir patekti į motinos pieną, todėl vaisius ir žindomas kūdikis gali būti veikiamas antidepresantų, skirtų motinai gydyti. Saugumo problemos skiriasi priklausomai nuo nėštumo laikotarpio ir pasirinkto antidepresanto. Gydymo antidepresantais neštumo ir žindymo laikotarpiu gairės aptartos kitur (Dodd ir kt., 2000a; Kennedy ir kt. 2009; Lam ir kt., 2009; Yonkers ir kt., 2009; Beyondblue 2011; Bauer ir kt., 2013; National Institute for Health Care ir Excellence, 2014) ir nėra šio sutarimo tema. Apskritai, depresijos gydymo pranašumai nusveria riziką vaisiui ar žindomam kūdikiui. Riziką galima sumažinti vadovaujantis aukščiau nurodytomis gairėmis.

Motinos kraujo plazmos ir pieno TMS gali būti atliktas, tačiau nėra būtinas. Nerekomenduojama kūdikiams matuoti antidepresantų koncentraciją atliekant kulno dūrio kraujo mėginius, dėl sukeliamo streso motinoms ir kūdikiams, ir antidepresantų koncentracija kūdikių kraujyje beveik visais atvejais yra žemiau žemiausios įprastinių analitinių metodų aptikimo ribos (Dodd ir kt., 2000b).

Jei pacientas vartoja antidepresantus, apie tai turėtų būti informuojama motinystės ir vaiko sveikatos tarnybos, kurios gali turėti protokolus atitinkamai situacijai spręsti. Vien antidepresantų vartojimas nėra pakankamas, kad būtų galima klasifikuoti nėštumą kaip didelės rizikos.

5.3 Senyvo amžiaus pacientai

Skiriant antidepresantus senyvo amžiaus pacientams sergantiems DS, reikia atsižvelgti į tai, jog jie taip pat dažniau serga ir fizinėmis ligomis, kurioms gydyti gali vartoti atitinkamus medikamentus. Inkstų ir kepenų funkcijos gali būti susilpnėjusios, todėl prieš pradedant gydymą gali reikėti jas ištirti. Pacientams reikia skirti amžių atitinkančią antidepresantų dozę ir stebėti, ar nėra nepageidaujamų reakcijų. Dėl padidėjusio antidepresantų veikiamų organų jautrumo ir sumažėjusio toleravimo rekomenduojamos mažesnės dozės (Cleare ir kt., 2015).

Tyrimais nustatyta jog SSRI, TCA, MAOI ir naujesni antidepresantai yra susiję su skirtingomis rizikomis senyvo amžiaus pacientams, tačiau nėra įrodymų jog tam tikra medikamentų grupė būtų susijusi su mažesne rizika šiai pacientų grupei (Couplandet ir kt., 2011). Naujesni antidepresantai ir SSRI, kurie laikomi saugesniu pasirinkimu suaugusiesiems, gali būti susiję su didesne hiponatremijos rizika vyresnio amžiaus pacientams (Coupland ir kt., 2011). Antidepresantų sukeltas delyras taip pat labiau tikėtinas senyvo amžiaus pacientams (Kogoj, 2014). Taip pat reiktų vengti antidepresantų, susijusių su ortostatine hipotenzija ar sedacija, dėl griuvimų rizikos (Williams ir kt., 2015). Yra negalutinių tyrimų duomenų apie antidepresantų vartojimą senyvo amžiaus pacientams, sergantiems demencija (Leong, 2014).

5.4. Gretutinės ligos

Duomenys apie pacientų, sergančių gretutinėmis somatinėmis ligomis, DS atpažinimą (Menear ir kt., 2015b) ir adekvatų gydymą (Menear ir kt., 2015a), yra prieštaringi. Somatinėmis ligomis sergantys pacientai, paprastai yra neįtraukiami į didelius klinikinius antidepresantų tyrimus, todėl šioje pacientų grupėje stebimas patikimų saugumo duomenų trūkumas. Vis dėl to keletas klinikinių antidepresantų tyrimų su pacientais, sergančiais specifinėmis somatinėmis ligomis, buvo atlikta. Tirti sergantys lėtiniu širdies nepakankamumu (O‘Connor ir kt., 2010), kur sertralinas nebuvo efektyvesnis už placebą, nepaisant ankstesnių efektyvumo įrodymų SSRI grupės medikamentais gydant depresiją su komorbidine išemine širdies liga (Rivelli ir Jiang 2007); Parkinsono liga sergantiems pacientams, SSRI ir SNRI buvo efektyvūs ir gerai toleruojami gydant gretutinį DS (Richard ir kt., 2012); Alzheimerio liga sergantiems pacientams sertralinas ir mirtazapinas nebuvo efektyvesnis už placebą (Banerjee ir kt., 2012). ŽIV infekcija sergančius pacientus gydant SSRI grupės antidepresantais stebėtas sumažėjęs kaulų mineralinis tankis (Mazzoglio y Nabar ir kt., 2015), tačiau nėra aišku ar šis poveikis susijęs su gydymu SSRI, ŽIV infekcija ar antiretrovirusiniu gydymu (Kruger ir Nell, 2017). Antidepresantų saugumas, dėl poveikio kaulų mineraliniam tankiui pacientams, sergantiems ŽIV infekcija, apima gydymo naudos ir žalos įvertinimą. Vis dėl to, yra pakankamai duomenų apie teigiamą antidepresantų poveikį gydant DS pacientams, sergantiems komorbidinėmis somatinėmis ligomis. (Ramasubbu ir kt., 2012).

5.4.1 Hepatinė ir renalinė disfunkcija

Hepatinė ir renalinė disfunkcijos susijusios su tam tikrais iššūkiais DS gydant farmakoterapija. Tam tikrais atvejais reikalingas medikamentų dozių sumažinimas. Tyrimo duomenimis, citalopramo dozės sumažinimas buvo nereikalingas pacientams sergantiems vidutinio sunkumo inkstų funkcijos nepakankamumu, bet būtinas esant sutrikusiai kepenų funkcijai ar sunkiam inkstų funkcijos nepakankamumui (Joffe ir kt., 1998). Nuo to, kiek medikamento ar jo metabolitų yra išskiriami per kepenis ar inkstus bei nuo inkstų ir kepenų funkcijos sutrikimo sunkumo priklauso ar reikės sumažinti medikamento dozę. Jei yra žinomi ar įtariami inkstų ar kepenų funkcijos sutrikimai, reikia patikslinti sutrikimo sunkumą.

5.4.2 Kaulų sveikata

Nėra pakankamai žinoma apie gydymo antidepresantais poveikį jau esant sumažėjusiam kaulų mineraliniam tankiui ar osteoporozei (Williams ir kt., 2016). Atkreipiamas dėmesys į medikamentus su mažesniu polinkiu stabdyti kaulinių ląstelių funkciją. Skirtumai tarp SSRI, pagal kaulo formavimosi ir funkcijos vystymosi stabdymą in vitro rodo sertraliną>fluoksetiną>paroksetiną>fluvoksaminą>citalopramą (Hodge ir kt., 2013); tačiau šiems laboratorinių tyrimų duomenims trūksta klinikinių įrodymų, todėl šių medikamentų poveikis kaulų sveikatai nėra visiškai aiškus. Sumažėjęs kaulų mineralinis tankis bei kaulinės masės netekimas nustatytas vartojant TCA bei kitų klasių antidepresantus (Rauma ir kt., 2016).

5.4.3. Kardiovaskulinės ligos

Prieš atsirandant naujausiems antidepresantams, pacientams, sergantiems išemine širdies liga, dažniausiai

būdavo skiriami TCA (Veith ir kt., 1982). Tačiau TCA gali sukelti QTc segmento pailgėjimą (Vieweg ir Wood, 2004) bei yra susiję su didesne atrioventrikulinės blokados rizika pacientams su Hiso pluošo kojyčių blokada (Roose ir kt., 1987). MAOI siejami su hipotenzijos ir tachikardijos rizika (Yekehtaz ir kt., 2013), retais atvejais su hipertenzinėmis krizėmis (Lavin ir kt., 1993), dėl to nėra rekomenduojami pacientams sergantiems kardiovaskulinėmis ligomis (CVD; Teply ir kt., 2016). SSRI ir SNRI pasižymi saugesniu kardiovaskuliniu poveikiu dėl to yra labiau tinkami pacientams, sergantiems kardiovaskulinėmis ligos; nepaisant to, yra klinikinių atvejų duomenų apie su SSRI vartojimu susijusia ortostatine hipotenzija, nežymia bradikardija, laidumo sutrikimais bei venlafaksino vartojimo sukeltą AKS padidėjimą, galimą QTc segmento pailgėjimą esant perdozavimui (Yekehtaz ir kt., 2013). Mirtazapino ir trazodono perdozavimas sukelia širdies funkcijos sutrikimus (Yekehtaz ir kt., 2013). Kardiovaskulines ligas gydantis gydytojas turi žinoti apie DS gydymui paskirtus medikamentus, bei vykdyti bendrą stebėjimą.

5.4.4. Endokrininiai bei autoimuniniai sutrikimai

Endokrininės funkcijos sutrikimai dažni žmonėms, sergantiems DS. Fizinio susirgimo adekvatus gydymas yra būtinas ir gali pagerinti ar net eliminuoti depresinius simptomus, pvz., esant skydliaukės funkcijos sutrikimui (Davis ir Tremont, 2007) ar sisteminei raudonąjai vilkligei (Karol ir kt., 2013). Antidepresantai turi poveikį pogumburio-hipofizės-anktinksčių ašies funkcijai, kortikosteroidų ir imuninei sistemoms, kurios sąveikauja su endokrininės funkcijos sutrikimais (Antonioli ir kt., 2012). Antidepresantai klinikinėje praktikoje dažnai skiriami esant gretutiniams endokrininės funkcijos sutrikimams kliniškai stebint pakankamą saugumą, tačiau tyrimų duomenų apie antidepresantų saugumą šiai asmenų grupei, trūksta.

5.4.5. Nutukimas

Daugumai pacientų, besikreipiančių dėl DS gydymo, stebimas viršsvoris arba nutukimas ir kai kurie antidepresantai gali būti susiję su tolimesniu kūno svorio didėjimu (Grundy ir kt., 2014). Tyrimų duomenys rodo, kad nutukimas yra susijęs su mažesniu atsaku į gydymą antidepresantais (Kloiber ir kt., 2007; Woo ir kt., 2016). Tyrimų duomenimis, su antidepresantais susijęs kūno svorio prieaugis yra reikšmingesnis moterims ir esant ilgesnei antidepresantų vartojimo trukmei (Bet ir kt., 2013). Yra esminių skirtumų tarp medikamentų. Nors SSRI siejami su kūno svorio augimu (Noordam ir kt., 2015), šis poveikis ryškesnis vartojant mirtazapiną (Bet ir kt., 2013) ir TCA (Berken ir kt., 1984). Tyrimo su elektroniniais sveikatos duomenimis nustatyta, jog bupropionas ir nortiptilinas mažiau susiję su kūno svorio prieaugiu nei citalopramas (Blumenthal ir kt., 2014), tačiau kito, 6 mėnesių trukmės atviro tyrimo metu nustatyta, jog nortriptilino vartojimas yra labiau susijęs su kūno svorio prieaugiu nei escitalopramo (Uher ir kt., 2009). Nenustatyta jog agomelatino vartojimas yra susijęs su kūno svorio prieaugiu (Demyttenaere, 2011) ir palyginamojo tyrimo duomenimis nebuvo nustatyta reikšmingų skirtumų svorio didėjimui lyginant agomelatiną ir SSRI (Demyttenaere ir kt., 2013). Duloksetino vartojimas, lyginant su kitais antidepresantais, svorio prieaugiui turi tokį patį (Blumenthal ir kt., 2014) arba mažesnį (Wise ir kt., 2006) poveikį nei lyginti antidepresantai. Pacientai, gydomi antidepresantais, turi būti informuoti apie kūno svorio augimo riziką bei supažindinti su svorio kontrolės ir mažinimo galimybėmis. Nutukimas yra susijęs padidėjusia kardiovaskulinių ligų rizika, dėl to TCA neturėtų būti skiriami.

5.4.6. Bipolinis sutrikimas bei afektinių epizodų rizika

Pacientai, sergantys nediagnozuotu bipoliniu sutrikimu, dažniausiai pirmą kartą kreipiasi gydymui esant depresijos epizodui. Šie pacientai gali patirti su antidepresantų vartojimu susijusius nuotaikų svyravimus, arba maniją arba hipomaniją. Jei stebimi mišraus epizodo simptomai, turi būti įtariamas bipolinis sutrikimas (Berk ir kt., 2015). Kadangi ši tema yra kompleksinė bei kontraversiška, ypatingai dėl diskusijų apie ribą tarp mišraus epizodo ir ažituotos depresijos, dėl to skaitytojai yra nukreipiami į šią temą atitinkančias apžvalgas (Swann ir kt., 2013; Ratheesh ir kt., 2017).

6. GYDYMO ANTIDEPRESANTAIS NEPAGEIDAUJAMŲ REIŠKINIŲ VALDYMAS

Pasireiškus nepageidaujamai reakcijai, sprendimas dėl gydymo keitimo turėtų būti priimamas individualiai. Reikia įvertinti tikimybę jog nepageidaujama reakcija yra susijusi su gydymu antidepresantu bei nepageidaujamos reakcijos sunkumą. Kuomet pasireiškia nepageidaujama reakcija, sprendimas dėl gydymo nutraukimo, dozės mažinimo ar gydymo tęsimo, turi būti priimamas nedelsiant. Esant sunkioms nepageidaujamoms reakcijoms, tokioms kaip medikamentų sukelta kepenų pažaida, skubus gydymo nutraukimas yra būtinas. Visos nepageidaujamos reakcijos turi būti aptariamos su pacientu ir sprendimai dėl gydymo priimami bendradarbiaujant.

6.1. Dažnos nepageidaujamos reakcijos

Nepageidaujamos reakcijos pasireiškiančios dažniau skiriant antidepresantus nei placebą yra pykinimas, galvos skausmas, nerimas, prakaitavimas, sedacija arba nuovargis, galvos svaigimas, ažitacija, svorio augimas, virškinimo sistemos sutrikimai bei burnos sausumas. Šie poveikiai gali būti praeinantys, tačiau šių poveikių trukmė nėra pakankamai ištirta ir gali skirtis tarp asmenų. Šių nepageidaujamų reakcijų pasireiškimas gali būti sumažinamas individualiai pasirenkant antidepresantą ir jo dozę (Ginsberg, 2009). Visos nepageidaujamos reakcijos susijusios su prastesniu pacientų gydymo režimo laikymųsi (Shelton, 2009). Vis dėl to, daugelis su antidepresantų vartojimu susijusių nepageidaujamų reakcijų atsiranda dėl nocebo efekto (Dodd ir kt., 2015), kuomet nepageidaujamos reakcijos yra nesusijusios su farmakologinėmis medikamento savybėmis. Gydymo režimo laikymuisi įtakos turi gydymo rizikos ir naudos su pacientu aptarimas, paciento įtraukimas į sprendimų dėl tolimesnio gydymo priėmimą (Shelton, 2009).

6.2. Lytinės funkcijos sutrikimai

Lytinės funkcijos sutrikimai yra dažna nepageidaujama reakcija, ypač susijusi su serotoninerginio poveikio antidepresantais ir pasireiškianti lytinio potraukio pakitimu, erekcinės, ejakuliacinės ir orgazminės bei kitų lytinių funkcijų sutrikimais (Taylor ir kt., 2013). Pacientų reikia reguliariai paklausti apie seksualinės funkcijos sutrikimus,

nes tai yra dažna medikamentų nevartojimo priežastis. Gydymo strategijos, esant seksualinės funkcijos sutrikimui, apima medikamento keitimą į turintį mažesnę seksualinės disfunkcijos sukėlimo riziką, psichologines ar mechanines intervencijas, „atostogas nuo medikamentų“, tačiau nėra pakankamai pagrįstos tyrimų duomenimis (Taylor ir kt., 2013). Klinikinio tyrimo metu patvirtintas teigiamas sildenafilo ar tadalafilo poveikis antidepresantų sukeltai seksualinei disfunkcijai vyrams ir bupropriono (150 mg du kartus per dieną) – moterims, koreguoti (Taylor ir kt., 2013). Vieno tyrimo duomenys rodo apie 5HT3 antagonisto granisetrono naudą (Berk ir kt., 2000), kuri pagrindžiama duomenimis, jog vortioksetinas, SSRI grupės antidepresantas, taip pat turintis poveikį į 5HT3, sukelia tik nežymią seksualinę disfunkciją (Jacobsen ir kt., 2016). Augmentacijos taktikos vyrams ir moterims apima SSRI augmentaciją mirtazapinu (Ozmenler ir kt., 2008) arba SSRI augmentaciją trazodonu (Stryjer ir kt., 2009). Stebėjimas dėl seksualinės disfunkcijos apima specifinių vertinimo skalių naudojimą, tokių kaip Arizonos seksualinių patirčių skalė (angl. *Arizona Sexual Experiences Scale, ASEX*) (McGahuey ir kt., 2000), Lytinės funkcijos indeksas (angl. *Sexual Functioning Inventory, SFI*) (Fava ir kt., 2011), Seksualinio funkcionavimo pokyčių klausimynas (angl. *Changes in Sexual Functioning Questionnaire, CSFQ*) (Clayton ir kt., 1997), Su psichotropiniais medikamentais susijusios seksualinės disfunkcijos klausimynas (angl. *the Psychotropic-Related Sexual Dysfunction Questionnaire, PRSexDQ-SALSEX*) (Montejo ir Rico-Villademoros, 2008) ir Lytinio poveikio skalė (angl. *the Sex Effects Scale*) (Kennedy ir kt., 2010).

6.3. Kardiotoksiškumas

TCA gali sukelti ortostatinę hipotenziją, tachikardiją, ŠSD pokyčius (angl. *heart rate variability*), intraskilvelinio laidumo sulėtėjimą ir yra susiję su didesne miokardo infarkto rizika (Marano ir kt., 2011) ir vaikų staigios kardialinės mirties rizika (Goldberg ir Ernst, 2012). Prospektyvio tyrimo duomenimis, asmenims, nesergantiems kardiovaskulinėmis ligomis, TCA vartojimas buvo susijęs su padidėjusia kardiovaskulinių ligų išsivystymo rizika po 8 metų stebėjimo laikotarpio (Hamer ir kt., 2011). TCA blokuoja kardiovaskulinius Na+, Ca2+ ir K+ kanalus ir sukelia QT intervalo pailgėjimą. Šie pokyčiai susiję su didesne torsade de pointes ir kitų susijusių aritmijų, kurios potencialiai yra mirtinos, išsivystymo rizika. Rizikos veiksniai yra vyresnis amžius, gretutinės kardiovaskulinės ir metabolinės ligos, įgimto ilgo QT sindromo šeiminė anamnezė, moteriška lytis, gretutinis metabolinių inhibitorių vartojimas bei hipokalemija (Vieweg ir Wood, 2004). Dėl to reikia atsargiai skirti medikamentus, galinčius pailginti QT intervalą, ypatingai dėl žinomų klinikinių rizikų. MAOI dažnai sukelia hipotenziją ir tachikardiją, bei gali sukelti hipertenzinę krizę (Yekehtaz ir kt., 2013). Naujieji antidepresantai yra saugesni širdžiai, bet kai kurie vis dėl to yra siejami su aritmijomis ir sinkope (Pacher ir Kecskemeti, 2004). Citalopramas priklausomai nuo dozės ilgina QT intervalą, todėl JAV FDA rekomenduoja daugiau nei 40 mg/p dozę skirti atsargiai (Pae ir kt., 2014). Nepageidaujamų kardiovaskulinių reakcijų valdymas turi būti atliekamas stebint AKS ir ŠSD. Papildomų medikamentų skyrimas taip pat yra svarstytinas. Sprendimas dėl paciento nukreipimo specialisto priežiūrai turi būti priimamas kiekvienu atveju individualiai (Goldberg ir Ernst, 2012).

6.4. Kepenų funkcijos sutrikimai

Visi antidepresantai yra susiję su medikamentų sukeltu kepenų pažeidimu, bet kai kurie medikamentai pasižymi didesne rizika nei kiti. Didžiausia kepenų pažeidimo rizika pasižymi nefazodonas (kai kuriose šalyse pašalintas iš rinkos), fenelzinas, imipraminas, amitriptilinas, duloksetinas, bupropionas, trazodonas, tianepinas, agomelatinas, o mažiausia – citalopramas, escitalopramas, paroksetinas ir fluvoksaminas (Voican ir kt., 2014; Friedrich ir kt., 2016). Medikamentų sukeltas kepenų pažeidimas dažniausiai pasireiškia per pirmuosius 6 mėnesius nuo antidepresantų vartojimo pradžios, nors latentinis periodas skiriasi tarp preparatų (Lucena ir kt., 2013). Kuomet stebimas padidėjusi serumo aminotransferazių koncentracija, ar pasireiškia kepenų funkcijos sutrikimo simptomai ar požymiai, antidepresantų vartojimą galime laikyti galima kepenų pažaidos priežastimi. Medikamentų sukelta kepenų pažaida gali būti hepatoceliulinė, cholestazinė arba mišri hepatoceliulinė-cholestazinė ir gali būti lengva, vidutinė arba sunki (Fontana ir kt., 2010). Pacientams, patiriantiems ūmų kepenų pažeidimą, gali pasireikšti nuovargis, pykinimas, pilvo skausmas, karščiavimas, tamsi šlapimo spalva, gelta arba odos niežulys (Fontana ir kt., 2010). Biocheminiai kepenų funkcijos tyrimai turi būti atliekami stebėjimui. Gali būti reikalinga specialisto priežiūra. Kitos kepenų pažaidos priežastys gali būti slaptas alkoholio vartojimas. Kai serumo transaminazių koncentracija normalizuojasi, gali būti sprendžiama dėl pakartotino antidepresanto skyrimo, pirmenybę teikiant ne kepenų funkcijos pažaidą sukėlusiam antidepresantui.

6.5. Hiponatremija

Hiponatremija apibrėžiama kaip būklė, kuomet serumo natrio koncentracija yra žemiau 135 mmol/l (Nagler ir kt., 2014), dažnesnė senyvo amžiaus asmenims bei gali pablogėti vartojant antidepresantus. Gydymo taktika priklauso nuo būklės sunkumo ir ūmumo. Visų gydymo taktikų tikslas yra atstatyti serumo natrio koncentraciją į normos ribas (Nagler ir kt., 2014). Skysčių ribojimas iki 1l per parą rekomenduojamas esant lengvai su antidepresantais susijusiai hiponatremijai (Goldberg ir Ernst, 2012). Taip pat siūlomas gydymo antidepresantais pertraukimas hiponatremijos gydymo laikotarpiu. Kitų medikamentų, ypatingai diuretikų, skyrimas taip pat svarstytinas. Alternatyva gydymui antidepresantais taip pat svarstytina.

6.6. Serotonino sindromas

Serotonino sindromas yra galimas perteklinio serotonino receptorių antagonizmo rezultatas ir nebūtinai yra idiopatinė reakcija (Boyer ir Shannon, 2005). Serotonino sindromas yra diagnozuojamas remiantis klinikiniais simptomais, sukeliamais CNS hiperjaudrumo kartu su medikamentų sukeltu serotonino pertekliumi. Simptomai skiriasi nuo lengvų iki gyvybei pavojingų. Dažni simptomai yra sumišimas, sąmonės sutrikimas, ažitacija, tremoras, hiperrefleksija, mioklonusas, tachikardija, hipertenzija ir karščiavimas. Esant sunkesniems atvejams pasireiškia rabdomiolizė, klonusas, rigidiškumas/hipertonusas, temperatūros pakilimas, karščiavimas arba hipertermija (Werneke ir kt., 2016). Serotonino sindromo gydymas visais atvejais apima serotoninerginių medikamentų

nutraukimą. Gydymo intensyvumas priklauso nuo būklės sunkumo, ir tam tikrais atvejais netaikant agresyvaus gydymo, paciento būklė gali blogėti. Kardiorespiratoriniai ir temperatūros sutrikimai turi būti nedelsiant koreguojami (Boyer ir Shannon, 2005). Ciproheptadinas yra rekomenduojamas serotonino sindromo gydymui, tačiau galimi ir kiti medikamentai (Boyer ir Shannon, 2005).

6.7. Kitos sunkios nepageidaujamos reakcijos

Žinomi ir reti, tačiau potencialiai gyvybei pavojingi šalutiniai antidepresantų poveikiai. Pranešta apie bent du mirtazapino sukeltos agranuliocitozės atvejus (Goldberg ir Ernst, 2012). Pasireiškus kraujo diskrazijai, jas sukėlęs medikamentas turi būti nutraukiamas. Antidepresantai yra susiję su padidėjusia traukulių rizika, ypatingai TCA ir bupropionas (esant didesnei nei 450 mg/p dozei), tačiau riziką galima sumažinti, sumažinus medikamento dozę (Mago ir kt., 2008). Antidepresantų sukelti ekstrapiramidiniai simptomai ir/ar akatizija yra reti nepageidaujami poveikiai, tačiau gali būti siejami su didesniu sergamumu ir sumažėjusia gyvenimo kokybe (Lane, 1998; Madhusoodanan ir kt., 2010). Pranešta apie gastrointestinalį kraujavimą pacientams, vartojantiems SSRI, kurie sutrikdo trombocitų funkciją (Bismuth-Evenzal ir kt., 2012), dažniausiai kartu vartojant aspiriną, nesteroidinius vaistus nuo uždegimo (NVNU) bei kitus medikamentus, veikiančius hemostazę (Mago ir kt., 2008; Anglin ir kt., 2015), taip pat antidepresantų ir NVNU kombinacija yra susijusi su didesne intracerebrinės hemoragijos rizika (Shin ir kt., 2015). Gastrointestinalinio kraujavimo prevencijai vartojant antidepresantus yra rekomenduojamas gretutinis protonų pompos inhibitorių ar H2 receptorių blokatorių vartojimas (Goldberg ir Ernst, 2012).

7. TYČINIO IR NETYČINIO ANTIDEPRESANTŲ PERDOZAVIMO VALDYMAS

Antidepresantų, ypač senesnių, tokių kaip TCA, perdozavimas gali būti mirtinas (Henry ir kt., 1995; Frey ir kt., 2000). Perdozavus TCA, gali pasireikšti traukuliai ir aritmijos. Staigus būklės blogėjimas yra dažnas ir mirtis ar sunkios komplikacijos dažniausiai pasireiškia per pirmas 24 valandas (Thanacoody ir Thomas, 2005). Naujieji antidepresantai yra saugesni esant perdozavimui. Mirtino toksiškumo indeksas (angl. *Fatal toxicity index, FTI*) yra mirčių skaičiaus dėl perdozavimo 1 milijonui receptų rodmuo, ir yra aukščiausias TCA – išdėstant nuo desipramino (FTI 201) iki amitriptilinino (FTI 38) ir MAOI tranilcipromino (FTI 44) (Buckley ir Faunce, 2003), žemesnis venlafaksinui (FTI 4.4) ir mirtazapinui (FTI 2.6) ir žemiausias SSRI – išdėstant nuo fluvoksamino (FTI 1.5) iki sertralino (FTI 0.38) ir fluoksetino (FTI 0.33) (Koski ir kt., 2013).

Skubus būklės valdymas esant perdozavimui priklauso nuo antidepresanto, jo metabolizmo ir pusinės eliminacijos laiko bei specifinių paciento veiksnių, tokių kaip kitų medikamentų ar alkoholio vartojimas perdozuojant. Gydymo taktika esant perdozavimui yra palaikomojo gydymo taikymas. Pirmo pasirinkimo gydymas yra absorbcijos mažinimas, skrandžio lavažas ar aktyvintos anglies skyrimas (Kerr ir kt., 2001). Esant TCA perdozavimui yra būtina alkalinizacija skiriant natrio bikarbonatą arba atliekant hiperventiliaciją (Kerr ir kt., 2001). Klinikinio atvejo duomenimis, natrio bikarbonato skyrimas gali turėti teigiamą poveikį esant venlafaksino perdozavimui (Buckley ir Faunce, 2003), tačiau duomenų, pagrįsti šiai gydymo taktikai esant kitų naujųjų antidepresantų perdozavimui, nepakanka. Su antidepresantų perdozavimu susijusių traukulių korekcijai gali būti taikoma oro takų apsauga ir benzodiazepinai (Buckley ir Faunce, 2003).

8. IŠVADOS

Gydymas antidepresantais gali būti susijęs su daugybe rizikų, reikalaujančių atidaus vertinimo ir stebėjimo. Gydymas antidepresantais turi apimti gydymo naudos ir žalos įvertinimą. Nepageidaujamos reakcijos gali būti sumažinamos remiantis saugumo stebėjimo rekomendacijomis, kas taip pat gali padėti nustatyti ir įvertinti nepageidaujamas reakcijas, joms pasireiškus. Nepageidaujamų reakcijų valdymo taktikos gali būti naudojamos norint optimizuoti pacientų gydymą. Saugus antidepresantų skyrimas apima individualių rizikos veiksnių atpažinimą ir šių rizikos veiksnių sąsajos su skirtingais antidepresantais, gretutiniais medikamentais ir kitų paciento veiksnių, įvertinimą.

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Learning to Deal with Problematic Usage of the Internet. Brussels : Cooperation in Science and Technology (COST) 2020. 28 p.

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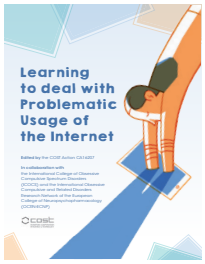

Could you imagine a day without an internet? It is hard, isn't it? Over the last few decades, the internet has become an inseparable part of our lives. The coronavirus pandemic strengthened the importance of internet even more – internet for many of us became the platform for our work and career, source of information, and place for communication with others; as well as a space of pleasurable activities, such as listening to the music, attending opera, watching movies, or playing games. Even supplying basic needs for household mostly relies on the usage of the internet. We are spending more and more time on the internet, but is there a line in which this "innocent' behaviour might become problematic? When should we became concerned about the time spend on the internet?

'Learning to deal with problematic usage of the internet' is a profound companion book written by a team of researchers working in European Research Network into Problematic Usage of the Internet, supported by COST (European Cooperation in Science and Technology), COST Action CA 16207 in a collaboration with multidisciplinary diverse group of experts from International College of Obsessive-Compulsive Spectrum Disorders (ICOCS) and the International Obsessive Compulsive and Related Disorders Research Network of the European College of Neuropsychopharmacology (OCRN-ECNP). The book aims to deeply analyse one of the most relevant, although highly underestimated psychological topics nowadays – problematic usage of the internet (PUI). While discussing the origins, expression forms and possible outcomes of problematic internet use, authors also provide practical expertise regarding PUI assessment tools, management strategies and simple everyday tips. By clearly communicating a biopsychosocial-approach-based framework of PUI, the authors successfully fulfil the primary purpose of this work, creating a comprehensible guide for the public, patients, family members and health care professionals.

The book begins with a comprehensive reflection on the phenomenon of problematic internet use. While having in mind that over the last few decades the internet became an integral part of our life, the authors analyse the distinction between beneficial internet use and the development of pathological online behaviours. Due to still relevant infancy of understanding the phenomenon, this book presents many of different forms of PUI expression, such as Internet-Related Gaming Disorder, Internet-Related Gambling Disorder, Internet-Related Buying-Shopping Disorder, Cyberchondria, Cyberpornography Addiction, Cyberbullying and Internet Social-Media/Forum Addiction. These paragraph-long sections discussing PUI subtypes contain carefully selected and concentrated information, disclosing the main determining factors and forms of problematic internet use, also highlighting relevant questions of this topic which still need to be studied. This focus offers rich notion for variety of possible PUI approaches of understanding and recognising problematic behaviour. Most importantly, although the text is comprehensively based on the scientific evidence and professional clinical expertise, authors use simple, clear, easily understandable language, pitched at the general reader rather than only the clinicians or the scientific community.

In addition to describing problematic usage of the internet, the book also reviews relevant diagnostic issues and the key tools regarding its' assessment. Emphasising the fine line between what is called 'normal' and 'problematic' internet use and with the consideration that PUI per se is not involved in any of diagnostic manuals, the authors first explain underlying factors leading to overall behavioural addictions (such as Gaming Disorder) and the diagnostic criteria for those forms of behaviour. With this approach, the hypothesis that PUI has similar underlying causes and expressions as other behavioural addictions is formed. Therefore, with this background knowledge it becomes easier to understand the possible symptoms or 'red flags' signalling about problematic online behaviour and choose appropriate tools for its' evaluation. The authors also provide brief description of various psychometric

instruments assessing different subtypes of PUI, established for both clinicians and patients or caregivers. Furthermore, having in mind that problematic usage of the internet does not usually appear as stand-alone issue, but rather co-occurs with other psychiatric disorders, the role of other psychological conditions like mood and anxiety disorders, obsessive-compulsive disorder, sleep disturbances and many others are discussed.

Within the last few sections of the book, the focus turns towards PUI management strategies. The authors acknowledge family environment as one of the most influential factors regarding the development of PUI. A healthy family involvement might play an important factor for effective preventive and management strategies of problematic internet use. Therefore, the book includes practical recommendations for caregivers about children's screen time use, based on different age groups and online activities. It is worth mentioning that by giving these recommendations, the beneficial aspects of online activities were also taken into consideration. With this approach, the book encourages caregivers to engage in parent-child communication, to negotiate on establishing rules and boundaries relating to the use of the internet, which would satisfy both parties. Finally, the book concludes reviewing evidence-based interventions regarding the prevention and management strategies of problematic usage of the internet, such as psychoeducation, psychological counselling, cognitive behavioural psychotherapy, etc. Although the high-quality evidence of these therapeutic options is still lacking due to methodological issues occurring in many clinical trials, the authors suggest that psychotherapeutic options, administered by trained professionals should be considered as first step of treating PUI.

In summary, the book should be considered as a complex analysis of a distinctive and relatively new phenomenon in today's digitalized world – the problematic usage of the internet. Though the book contains carefully selected scientific and clinical information regarding the development, expression, assessment, and management of PUI, it is written in 'reader-friendly' style, which allows to extend the knowledge of PUI not only for scientists or health care professionals, but also patients, families, schoolteachers, and public.

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Aidana Lygnugaryte-Griksiene – Skills for Suicide Intervention by Emergency Medical Care Doctors, Nurses and Factors Affecting them

Aidana Lygnugaryte-Griksiene. A psychiatrist – psychotherapist. Aidana specializes in crisis management and in the field of suicide interventions and management. In 2020 defended her PhD thesis extramurally. Aidana is working as a psychiatrist in Palanga Hospital at LUHS Neuroscience Institute.

INTRODUCTION

The World Health Organization declares: currently, suicide is one of the three most common causes of death for people aged 15–44 in the world. Around 1 million people worldwide commit suicide each year. According to the WHO, Lithuania is the leading country in terms of suicide rates in Europe and fifth in the world. The number of suicides in Lithuania has decreased significantly over the last twenty years, from more than 45 to nearly 30 cases per 100,000 residents. A particularly significant decrease in the number of suicides was registered in 2005–2008. In subsequent years the indicator stabilized. Currently, the suicide rate in the country is almost 3 times higher than the European Union average. Non-fatal suicide attempts are 10 times more frequent and require urgent medical attention. Among them, the risk of fatal suicide is three times higher than in the general population. Suicide is one of the most dangerous risk factors for human health in Lithuania and requires effective prevention measures.

Five key areas of suicide prevention have been identified: suicide prevention training programs, methods for screening high-risk individuals, treatment of mental disorders, restriction of access to lethal measures, presentation of information about suicide in the media. One of the promising interventions in suicide prevention is the training of health care professionals. Emergency medical care (EMC) professionals, who are closest to potentially vulnerable individuals, can identify those at risk for suicide, provide initial support, and direct them to further assistance. The actions of the EMC professionals largely depend on what kind of help the patient will receive. EMC professionals, when confronted with persons committed suicide or attempt to commit suicide, experience stress that psychologically has a significant negative impact on themselves. The mental health of EMC professionals is important, as well as their ability to recognize their own stress situations and symptoms indicating burnout syndrome, mental health disorders. This can significantly impair the mental health of EMC professionals and impair their ability to do their job.

AIM

To evaluate the skills for suicide intervention by EMC professionals and the factors affecting them.

OBJECTIVES

1. To evaluate the association between sociodemographic factors of EMC professionals and suicide intervention skills.
2. To evaluate the attitudes of EMC professionals towards suicide and their association with sociodemographic factors and suicide intervention skills.
3. To evaluate the manifestation of burnout syndrome among EMC professionals and its association with sociodemographic factors and suicide intervention skills.
4. To evaluate the mental health of EMC professionals and its association with sociodemographic factors and suicide intervention skills.
5. To evaluate the impact of suicide intervention training on the suicide intervention skills, attitudes, burnout syndrome expression, and mental health of EMC professionals.

CONCLUSIONS

1. Better suicide intervention skills of EMC professionals prior to training were associated with younger age (<45 years), shorter length of service in health care system (<15 years), higher education, and the physician profession. Lower suicide intervention skills for EMC professionals prior to training were associated with older age (>55 years), longer length of service in health care system (>30 years), vocational education, and the nursing profession.
2. Better suicide intervention skills among EMC professionals were associated with more positive attitudes toward suicide; more positive attitudes were associated with the profession of physician and with shorter length of service in health care (<15 years).
3. More than a third of EMC professionals had a high burnout degree before training. High burnout degree occurred in EMC professionals with better suicide intervention skills. Younger EMC professionals (<45 years) who had shorter length of service (<15 years) were more likely to experience depersonalization. EMC professionals with longer length of service (>30 years) were less emotionally depleted than EMC professionals with shorter length of service (<15 years). Physicians' emotional exhaustion was significantly higher than that of nurses.
4. Generalized anxiety disorder was found in more than half of EMC professionals surveyed, more than one-eighth in suicide risk, ten per cent had a current depressive episode, and six per cent had harmful alcohol consumption. Harmful alcohol consumption was more common among older EMC professionals (>55 years). EMC professionals had a suicide risk before training also had significantly better suicide intervention skills.
5. Suicide intervention training had a generally positive but different effect depending on the age of the subjects. Senior EMC professionals (>55 years) demonstrated improved suicide intervention skills after training, with a reduction in their overall burnout syndrome, suicide risk, and generalized anxiety disorder. Younger EMC professionals (<45 years) showed worse suicide intervention skills after training, but there was reduced their burnout syndrome, suicide risk, and generalized anxiety disorder.

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