Anxiety symptoms in depression: are they related to antidepressant treatment and its side-effects?

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Subject: Psychology
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Title: Anxiety symptoms in depression: are they related to antidepressant treatment and its side-effects?
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Abstract: Earlier studies suggest that depression with comorbid anxiety symptoms have worse treatment outcomes, but that anxiety symptoms could be alleviated with antidepressants (AD). Depressed patients with comorbid anxiety symptoms also suffer from more severe and frequent AD side effects, but less is known about associations between anxiety and specific side-effects (e.g. sexual and withdrawal side-effects). The two aims in the present study were (1) to elucidate associations between anxiety symptoms and AD treatment, and (2) investigate the association between anxiety symptoms and perceived side effects of AD treatment. Data for the present study was extracted from the DETRECO project (N = 326; 18-63 years), where 137 respondents were currently under AD treatment, and 189 respondents had never been under AD treatment. The AD users were significantly older than the non-users and a higher percentage of the AD users had been depressed for five years or more. Women were also slightly overrepresented in the AD users. Anxiety levels were measured using STAI-6 and AD treatment was assessed with specific questions on usage. Perceived side effects of AD were addressed with a questionnaire. Exploratory factor analysis data from Sjöberg (2017) was utilised for computing mean scores in four side effects factors. The results of a two-way ANCOVA showed no significant main effect of either treatment (AD vs. no AD) or depression duration (0-4 vs. ≥ 5 years) on anxiety symptom levels when controlling for age, but a significant main effect of the covariate age was found. A subsequent control analysis of age-matched participants revealed no differences in anxiety levels. In the second part of the study, multiple hierarchical regression analysis found a significant negative association between anxiety and sexual side effects, such that higher anxiety levels were associated with lower levels of sexual side effects. Estrangement, Dependency/Abstinence or Physical side effects were not associated with anxiety. To conclude, no difference was found in anxiety level between those who were and were not under AD treatment. Nonetheless, an unexpected negative association was found between anxiety and sexual side effects, which may be due to anxiety distracting attention from erotic cues and in turn decreasing overall sexual activity and resulting in less sexual side effects experienced.
Keywords: Antidepressants, depression, anxiety, side effects.

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ÅBO AKADEMI - FAKULTETEN FÖR HUMANIORA, PSYKOLOGI OCH TEOLOGI

Ämne: Psykologi
Författare: Sally Lo
Titel: Ångestsymtom i depression: är de relaterade till antidepressiva läkemedel och läkemedlens biverkningar?
Handledare: Mira Karrasch
Abstrakt: Enligt tidigare studier kan depression med komorbida ångestsymtom resultera i sämre behandlingsutfall jämfört med endast depression, men ångestsymtom kan lindras med hjälp av antidepressiva läkemedel (AD). Deprimerade patienter med komorbida ångestsymtom kan även ha en ökad risk för mer och svårare biverkningar av AD. Dock är kunskapen begränsad gällande associationerna mellan ångestsymtom och specifika biverkningar (av t.ex. sexuell och abstinent karaktär). Syftet med denna avhandling var att studera associationerna mellan ångestsymtom, AD-behandling och dess upplevda biverkningar. Data från DETRECO projektet (N = 326; 18-63 år) användes för att besvara frågeställningarna. Av deltagarna använde 137 AD, medan 189 aldrig använt AD. Kvinnor var en aning överrepresenterade och signifikant äldre i AD-gruppen än de som aldrig använt AD, men ingen skillnad mellan grupperna fanns gällande depressionssvårighet (QIDS-SR) eller utbildningsnivå. Ångestsymtom undersöktes med STAI-6 och antidepressiv behandling utvärderades med specifika frågor kring användning. Upplevda biverkningar av AD undersöktes med ett frågeformulär. Explorativ faktoranalytisk data från Sjöberg (2017) användes för att utforska medelvärden i fyra biverknings-faktorer. Resultaten från en 2 x 2 ANCOVA fann ingen signifikant huvudeffekt av antingen behandling (AD vs. icke-AD) eller depressionkronicitet (0-4 vs. ≥5 år) på ångestsymtom, kovariatet ålder var däremot signifikant. En kontroll-analys med åldersmatchade grupper utfördes och påvisade inte heller någon signifikant skillnad i ångestsymtom mellan grupperna. I andra delen av avhandlingen gjordes en multipel hierarkisk regressionsanalys av biverkningar. Då fanns en negativ korrelation mellan ångestsymtom och sexuella biverkningar där högre ångest var associerat med mindre risk för upplevda sexuella biverkningar. Dock korrelerade inte ångestsymtom med resten av biverkningarna: Utanförskap, Beroende/Abstinens och Fysiska biverkningar. Sammanfattningsvis konstaterades att inga skillnader i ångestsymtom fanns mellan AD- och icke-AD-gruppen. En oväntad negativ association konstaterades mellan ångest och sexuella biverkningar vilket eventuellt kan förklaras av att ångest distraherar individens uppmärksamhet från erotiska signaler och på detta sätt minskar sexuella aktiviteter överlag, vilket leder till mindre upplevda sexuella biverkningar.
Nyckelord: Antidepressiva, depression, ångestsymtom, biverkningar

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Anxiety symptoms in depression: are they related to antidepressant treatment and its side-effects?

Depression is one of the most common mental disorders in the world, affecting about 264 million people worldwide in 2017 (GDB Disease and Injury Incidence and Prevalence Collaborators, 2017). It is ranked as the single major contributor to global disability and the largest contributor to suicide death (World Health Organisation, 2017). Finland tops the prevalence of mental disorders in Europe with rates of 18.8% of the population suffering from some kind of mental illness, along with depression as the most common mental disorder in the last few decades (The Organisation of Economic Co-operation and Development, 2018; OECD). Various studies conducted between 1996 and 2011 have reported rates up to 9.3% of the Finnish population suffering from depression (Lindeman et al., 2000; Markkula et al., 2015; Pirkola et al., 2005). The incidence of disability pensions has also increased until the late 2000s (Honkonen & Gould, 2009 as cited in Markkula et al., 2015), and earlier retirements are increasingly more due to depression (Karpansalo et al., 2005).

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013), Major depressive disorder (MDD; referred to as depression in the current study) presents symptoms such as depressed mood or anhedonia, appetite or weight changes, sleeping difficulties, cognitive dysfunctions, feelings of worthlessness and more. Although not included, anxiety symptoms are common in depression (Montgomery, 2019), and are suggested to co-occur in up to 78% of depressed patients (Gaspersz, Nawijn, Lamers & Penninx, 2018). The most common treatment for depression in Finland is antidepressant (AD) medication (Honkonen, Aro, Isometsä, Virtanen & Katila, 2007) which has been suggested to be as effective in depressed patients with anxiety symptoms (e.g. Lyndon, Prieto, Wajsbrot, Allgulander & Bandelow, 2019). Nonetheless, AD has been shown to have side effects (Ottosson, 2018), which are argued to be even more burdensome when anxiety is present in depression (Ionsescu, Niciu, Richards & Zarate, 2014). However, the extent of AD side effects are suggested to be suppressed by publication bias, and their true prevalence has possibly been underestimated (Bet, Hugtenburg, Pennix & Hoogendijk, 2013; Popovic, Vieta, Fornaro & Perugi, 2014; Turner, Matthews, Linardatos, Tell & Rosenthal, 2008). The present study set out to examine whether anxiety symptom levels would differ between depressed individuals using ADs and those who have never used ADs. Possible associations between anxiety symptoms and side-effects of ADs are also examined in the subset of participants who are using ADs.

1.1 Anxiety symptoms in depression

Trait anxiety is the stable and personality-related tendency to attend to worrisome and fearful parts of many situations (Derakshan & Eysenck, 2009; Eysenck, 1992; Gidron, 2013). State anxiety is defined as a subjectively high perceived threat to the individual. It is the interaction between trait anxiety and situational stress and is experienced as strong emotions of worry and fear. State anxiety will be of focus in the current study.

Anxiety symptoms in depression are suggested to result from, among others, feelings of guilt, hopelessness and low physical well-being (Ottosson, 2018). Anxiety is suggested to be a commonality in depression (Wiethoff et al., 2010) and various studies have estimated that between 42-80% of adults with depression have anxiety symptoms of clinical significance (Gaspersz et al., 2018; Lyche, Jonassen, Stiles, Ulleberg & Landrø, 2010; Zimmerman et al., 2000). A recent meta-analysis suggested that all types of anxiety symptoms predicted later depressive symptoms and vice versa; the two having a "bidirectional prospective relationship with one another" (Jacobson & Newman, 2017, p. 1169). Nonetheless, few studies have investigated patients who have depression but also manifest anxiety symptoms as they often are excluded from clinical trials due to their comorbidity (Zimmerman, McDermus & Mattia, 2000). Yet, they are argued to be a more vulnerable (as well as a more prevalent) clinical group since depression with anxiety symptoms or anxiety disorders are suggested to present a greater challenge in treatment (Montgomery, 2019).

Anxiety is argued to be associated with poorer clinical outcomes (Gaspersz et al., 2018) and a higher risk of suicidality (Allgulander, 2000, as cited in Lyndon et al., 2019). Comorbid depression with anxiety symptoms is suggested to be associated with negative cognitive outcomes such as deficits in cognitive-emotional processing (e.g. negative attentional bias; Mathews, Mackintosh & Fulcher, 1997), inhibitions and attention shifting (Braund et al., 2019; Derakshan & Eysenck, 2009). Compared to patients with depression only, patients with depression and anxiety are more likely to have greater depression severity, longer duration of depression, greater psychosocial disability, higher risk of relapse (Altamura, Montresor, Salvadori & Mundo, 2004; Fava et al., 2006; Lyche et al., 2010; Weiss et al., 2016; Wiethoff et al., 2010) and reduced quality of life (Gaspersz et al., 2018; Ionescu, Niciu, Henter & Zarate, 2013). In a relatively recent study by Cha and colleagues (2018), the researchers found that participants with depression reported significantly more symptoms of anxiety assessed by Generalised Anxiety Disorder-7-items (GAD-7), compared

to healthy controls. The depressed participants were however under AD treatment, thus a comparison with a depressed group not using AD was lacking. Additionally, a longitudinal study conducted by Weiss et al. (2016) investigated 298 women (19-90 years old) with mood disorders and examined factors such as age, physical morbidity, hormonal status and anxiety symptoms. Levels of anxiety in women with moderate depression were the strongest predictor of severe depression, including thoughts of death and suicide. But age and hormones, perhaps counterintuitively, were not significant predictors of severe depression. These findings suggest the need for priority of addressing anxiety symptoms in the treatment of depression.

1.2 Antidepressant treatment and its prevalence

AD medication is a common treatment for depression (Honkonen et al., 2007; National Institute for Health and Clinical Excellence, 2004). Moore and colleagues (2009) reviewed a UK patients register of over three million people and found that about 81% of patients diagnosed with depression received at least one prescription of AD within the first year of diagnosis. More than a dozen different types ADs in the US have suggested effectiveness for treatment of depression (Drobizhev, Fedotova & Kikta, 2015). Selective Serotonin Reuptake Inhibitors (SSRIs) are the most common medication of choice (Ottosson, 2018) and the frequency of people maintaining AD treatment for longer than five years has increased since 1994 (Lockhart & Guthrie, 2011; Moore et al., 2009).

This long-term usage trend has also been observed in Finland and with significant increase from 1995 to 2000 (Sihvo et al., 2010). AD as a choice of treatment is even more common in Finland than in Europe in general (OECD, 2014). Honkonen et al. (2007) investigated treatments for depression in Finland utilising two national representative samples with a ten-year interval (1993-1994 to 2003-2004). They found that only about 10.6% of the patients with depression had received psychotherapy weekly, while 85.6% got AD treatment, leaving AD treatment as the most utilised depression treatment in Finland. On the same note, a later study found that 8.3% of the general Finnish population had been prescribed ADs (Vilhelmsson, 2013), with AD being the seventh most prescribed type of medication in Finland in 2016 (The Social Insurance Institution of Finland, 2016, as cited in Sjöberg, 2017).

1.3 Antidepressant treatment, depression and anxiety symptoms

Varying levels of anxiolytic effects of ADs exist (Ottosson, 2018). A meta-analysis on AD treatment proposed that anxiety significantly decreased following AD treatment in randomised placebo-controlled trials (Nelson, Portera & Leon, 2005). In a study by Cha et al. (2018) 100 individuals with depression under AD treatment were compared to healthy controls, all between the ages 18-65. Participants were measured on their anxiety symptoms using GAD-7, and it was found that the depressed group with both high and low anxiety benefited significantly more following AD treatment, compared to healthy controls.

A recent meta-analysis of placebo-controlled studies (N = 2405; Lyndon et al., 2019) investigated whether participants with higher or lower levels of anxiety symptoms were affected differently by AD treatment (6-12 weeks treatment). Based on anxiety scores from the Hamilton Rating Scale for Depression (HAM-D), patients with depression were divided into either a low (<3) or high anxiety (≥ 3) group. The results suggested that following AD treatment (1) both the low- and high-anxiety groups had a significantly greater decrease in anxiety compared to the placebo group, and (2) the group with high anxiety had a significantly greater decrease of anxiety compared to the low-anxiety group. Thus, suggesting that AD treatment had great anxiety-relieving associations in depressed patients with both low, but especially high anxiety. Thereupon, the authors stressed the importance of assessing anxiety in depression treatment and adapting AD treatment accordingly as some ADs are suggested to be more efficient in depression with comorbid anxiety symptoms than others.

1.4 Anxiety and side effects of antidepressant treatment

According to the American Psychological Association's revised Practice Guidelines for the Treatment of depression (2019), AD treatment should be, among others, chosen based on its potential side effects. Some common cognitive AD side effects are fatigue, memory impairment and inattentiveness (Popovic et al., 2015). Impaired verbal memory has been found in both current users and remitted users of AD (Nagane et al., 2014). Physical side effects such as withdrawal, sexual problems and weight gain have been found in a study on 180 long-term users of AD. They did also report emotional side effects like feeling emotionally numb and addicted. Although reporting feeling satisfied with the AD, the patients did find side effects concerning (Cartwright, Gibson, Read, Cowan & Denhar, 2016). Similar side effects were found in a study on long-term AD use completed by 1829 adults in

New Zealand, with additions such as feeling not as themselves, reduction in positive feelings, caring less about others and suicidality (Read, Cartwright & Gibson, 2014).

Side effects of AD treatment are suggested to be elevated when anxiety is present in depression (Fava et al., 2008; Ionescu et al., 2014). There is again limited earlier research on side effects in AD treatments for depression and anxiety symptom comorbidity, where most studies have instead focused on anxiety disorders rather than symptoms (Hung et al., 2020). A study by Shankman et al. (2017) examined whether depressed patients with comorbid panic disorder experienced more side effects than those without panic disorder. The study suggested a higher frequency of side effects reported in the group with comorbidity.

Moreover, researchers have begun looking into the term *anxious depression* which is in broad terms defined as high levels of anxiety (≥ 7score on HAM-D) within depression (Ionescu et al., 2013). It has been suggested that it affects up to 50% of patients with depression (Fava et al., 2008). A review on AD treatment on anxious depression found that these patients were at a greater risk for side effect burden (Ionescu et al., 2014). An earlier study by Fava et al. (2008) found similar results where patients with anxious depression reported higher frequency, intensity, and burden of side effects. They also reported significantly more serious adverse events.

1.5 Publication bias of AD treatment efficacy and side effects

It has been argued that publication bias has resulted in an overestimation of AD treatment efficacy and underestimation of its side effects. This is often explained as being linked to financial conflicts of interest as it is assumed that most clinical trials are sponsored by the medical industry (Ebrahim et al., 2016; Fava et al., 2016). According to Turner et al. (2008), 94% of the published literature on AD medication were positive findings, whereas only half of all trials had positive results on the pre-registered primary outcome, i.e. negative trials were not published. Clinical trials are also argued to underreport side effects (Bet et al., 2013; Popovic et al., 2014) or not assess them appropriately (Rief et al., 2009). The reported AD treatment trials also mainly examine short-term use (6-8 weeks), while the limited published long-term trials are between 6-12 months use which is still shorter than the general length of time for AD treatment (Bet et al., 2013; Ferguson, 2001). It has also been argued that there is limited use of objective measures of side effects in the published studies (Gartlehner et al., 2008).

1.6 The present study

The general aim of the study was to elucidate the association between anxiety symptoms and antidepressant treatment. First, the association of AD treatment and anxiety symptom levels were of interest. The study by Cha et al. (2018) assessed anxiety symptoms during AD treatment but lacked a depressed group not under AD treatment to compare with. The current study aimed to fill that gap by comparing the anxiety symptom levels of depressed patients using and not using AD. Hence, based on previous research (e.g. Lyndon et al., 2019; Nelson et al., 2005), it was expected that depressed individuals would be more likely to have lower levels of anxiety symptoms following any type of AD treatment, in comparison to depressed individuals not under AD treatment.

The second aim of the study was to explore the associations between anxiety symptom levels and AD side effects. Based on limited previous research, it has been suggested that there is a higher likelihood of experiencing more side effects from AD treatment when the patient has higher anxiety (Fava et al., 2008; Ionescu et al., 2014). Thus, in the current study, it was expected that within the group of depressed individuals under AD treatment, higher levels of anxiety levels would be associated with more severe side effects of AD.

Method

The data collection was a part of a study project at Åbo Akademi called Depression Treatments and Cognitive functions (DETRECO). It was conducted between 2015 and 2017, with ethical permission by the Board of Ethics at the Department of Psychology at Åbo Akademi University. The primary aim of the DETRECO was to investigate depression and cognitive functions.

2.1 Participants

The original data set had 491 respondents. 105 respondents were excluded due to not indicating depressive symptoms or incompletion of the survey. The majority who discontinued the survey stopped very early on, thus drop-out analyses on specific features of these participants would not have yielded any meaningful results as e.g. demographic information was missing from many of the drop-outs.

The current study initially included 386 individuals. Some respondents (n = 60) reported that while they were not currently using ADs, they had used AD previously, these respondents were excluded from analyses. This resulted in two AD groups, one currently under AD treatment (n = 137) and one which had never had AD treatment (n = 189), in total 326 respondents. These respondents had completed the full survey and indicated subjective experience or a diagnosis of depressive symptoms. A few respondents (n = 4) were above the age limit (55 years) of the study, but they were included in the analysis as cognitive outcome was not the focus in the present study (the age-limit in DETRECO was set at 55 years in order to ensure that no participants with preclinical dementing syndromes would be included).

Respondents were between 18-63 years old (M = 28.66, SD = 9.02). There was a statistical significant difference in age between those who never had AD treatment (M = 25.70, SD = 6.17) and those who were using AD treatment (M = 32.74, SD = 10.63), $t(201.92) = -6.96$, $p < .001$, $d = 0.81$. There were 65 males, 250 females, 5 transgender respondents and 6 responded “other” in total and included in the main analyses. Analysing gender distribution as a dichotomous variable (female/male) showed that there was a significant difference between the AD users and non-users, $\chi 2(1, N = 315) = 5.96$, $p = .015$. There was a slight overrepresentation of females in the AD user group (81%) compared to females in the AD non-user group (73%). No differences between the AD users and non-users were observed in depression severity as measured by QIDS-SR, $t(377) = -.537$, $p = .592$, $d = 0.002$ or levels of education, $t(324) = .75$, $p = .457$, $d = 0.09$. There was a significant difference in depression duration between the AD users and non-users, as longer depression duration (≥5 years) was more frequent among the AD users, $\chi^2(1\ N = 311) = 20.18$, $p < .001$. Polypharmacy was also relatively frequent, 45% of AD users reported having at least one other psychotropic medication. Demographics data are shown in Table 1.

Table 1

Population demographics and clinical data on sample currently under AD treatment and sample not under AD treatment (N = 326)

	AD users (n = 137)	AD non-users (n = 189)	
Characteristics	*M (SD, min-max)*	*M (SD, min-max)*	Stat. sign
Age[1]	32.74 (10.63, 18-63)	25.70 (6.17, 18-51)	$p < .001$†
Gender			$p = .015$■
Female	111	139	
Male	18	47	
Transgender	5	0	
Other	3	3	
Education			n.s.°
Elementary school	5	0	
Vocational school	21	5	
Upper secondary school	47	105	
Polytechnic	22	18	
Bachelor's degree	26	50	
Master's degree	13	8	
Doctoral degree	2	1	
Other	1	2	
Depression severity (QIDS-SR)	14.07 (5.29, 0-26)	14.06 (4.25, 0-23)	n.s.†
Duration of depression			$p <.001$■
0-4 years	47	111	
≥5 years	84	69	
Duration of AD use			
Up to 1 year	38%	NA	

1 - 4 years	19%	NA
≥5 years	43%	NA
Psychoactive drugs used[2]		
1 AD only	55%	NA
1 AD + at least 1 other psychoactive drug[3]	45%	NA

Note. [1] Although the initial range was set at 18-55, respondents over the age of 55 (n = 4) were included in the analyses. [†]Spearman's Rank Correlation Coefficient, ▪ Chi-Squared Test, ◦Mann-Whitney U Test, [2] missing 21 respondents due to not responding to questions, [3]most common were other antidepressants, benzodiazepines, sleeping pills, anxiolytics and antipsychotics.

2.2 Procedure

Utilising convenience sampling, participants were recruited through advertisements at various health care centres in Finland, internal recruitment adverts at Åbo Akademi University, at the Student Health Care Unit in Turku, along with social media (e.g. Facebook). The study was conducted online using SOILE, a testing platform developed by Brain Train Research Centre of Excellence at the Department of Psychology, Åbo Akademi University.

DETRECO included a survey and a working memory test, all in Finnish. The survey included questions and questionnaires on demographics, functional ability, physical health, coping skills, personality, subjective cognitive impairment, depression, anxiety, medication, other treatments, and causes of depression. The study could be completed at any computer available for the participant, however preferably at home, and took approximately one hour to complete. Participants were asked to only participate if they were between the ages of 18-55 years and had subjective or diagnosed symptoms of depression.

2.3 Instruments

With its extensive set of questions, the DETRECO survey provided the current study with data on demographics, depression severity, anxiety symptoms levels, and questions on

depression such as duration, AD treatment and its side effects. The demographics obtained were age, gender, and educational level.

Three self-assessment scales were used. One was the *Quick Inventory of Depressive Symptomatology 16 items* (QIDS-SR (16); Rush et al., 2003; Appendix A) which measures depression severity. Each item was scored on a scale of 0-3 with varying responses gradually increasing in severity in each item. The severity of depression was regarded as 0-5: none, 6-10: mild, 11-15: moderate, 16-20: severe and 21-27: very severe.

The second self-assessment scale was the six-item short-form of the state anxiety scale Spielberger *State-trait Anxiety Inventory* (STAI-6; Marteau & Bekker, 1992; Appendix B). The items encompass three anxiety-present (nervous, upset and worried) and three anxiety-absent (calm, relaxed and satisfied) questions. They were rated on a scale from 1 (*Not at all*) to 4 (*A lot*). This shorter version was selected to limit the length of the already extensive DETRECO survey. Originally with 40 items, the six-item form gained an acceptable reliability coefficient of $\alpha = 82$, the items were highly correlated, $r = .91$, and produced scores similar to full-form, $t(22) = .96$, $p = .35$ (Marteau et al., 1992). In the present study, positive STAI items were reversed so that a larger score indicated more anxiety symptoms, and therefore a sum score of the responses on all six items was calculated. Consequently, the range of the summative score was 4-24.

The third questionnaire was a 20-item questionnaire on benefits and adverse effects of AD treatment developed by Read, Cartwright and Gibson (2014; Appendix C). It included both physical and psychological side effects and a response scale ranging from 1 ("*Not at all"*) to 4 ("*Difficult/A lot"*). An exploratory factor analysis on this data was conducted by Sjöberg (2017), exploring potential underlying factors and mean scores for each factor. The Principal Axis Factor (PAF) with an Oblique rotation was utilised in the analyses to allow factors to correlate. Out of the 20 items, seven factors were extracted with loadings over .3, explaining 45.77% of the total variance. Two of the side effects items had loadings less than .3 (diarrhoea and headache). Based on the Cronbach's Alpha, four side effect factors or, as Sjöberg called them, clusters, were left with enough reliability. These were later investigated and analysed in the current study. More information on the factor loadings can be found in Sjöberg (2017).

Moreover, a question investigating duration of depression was included ("*How long have you been depressed?*") with response options on a seven-point scale varying from "*under a year*", "*1-2 years*", "*3-4 years*" and so on up to "*more than 10 years*". Checking the distribution of depression duration amongst the participants showed a bimodal distribution,

with peaks at "*1-2 years*" and "*over 10 years*" of depression. Thus, to ease the interpretation of results and control for depression duration in the main analysis, the variable was transformed to having two levels: "*0-4 years"* and "*5 years and more".*

Usage of AD treatment was tapped with one question ("*Do you use antidepressant medication?*") and provided participants with four response options ("*Yes*", "*Never*", "*Yes, but not anymore*", and "*I have a prescription but have not used it*").

2.4 Study design and data analysis

Statistical analyses were performed using IBM SPSS Statistics 26.0 for Windows (IBM Corp., 2019). In all analyses, alpha level was set to $p < .05$.

Addressing the first study questions, with a between-subjects design, the aim was to compare anxiety levels between those who were vs. were not under AD treatment. A univariate 2 x 2 ANCOVA was conducted to examine effects of antidepressant use (yes/no) and duration of depression (</> 5 years), as independent variables (IV), on anxiety levels as the dependent variable (DV). Age was used as a covariate to control for possible confounds as there was a statistically significant difference in age between the AD users and non-users. It was first expected that there would be a main effect of antidepressant use so that the group currently under AD treatment would report lower levels of anxiety compared to the group which never had AD treatment. It was also expected that there would be no main effect of duration of depression on anxiety levels. A follow-up 2x 2 ANOVA examining the effect of antidepressant use (yes/no) and duration of depression (</> 5 years) with a subset of participants who were 30 years or younger, without using age as a covariate, was run as a secondary control for age-confounding.

It was also expected that within the group currently under AD treatment, anxiety levels would be associated with side effects reported, and the higher anxiety levels would be related to higher side effects burden. Here, anxiety level was again the DV to be predicted by four IVs, which were side effect factors from the DETRECO-based study by Sjöberg (2017). These were: Estrangement, Sexual, Dependency/Abstinence and Physical side effects. Thus, to address the second study question, four hierarchical regression analyses were conducted for each of the four side effect mean scores in the subset of the sample who were using antidepressants (n = 137). In step one, age and depression severity (QIDS-SR) were entered

as predictors and in step two, anxiety level (STAI-6) was added as a third predictor. Other variables controlled for all the analyses were gender and educational level.

Results

3.1 Differences in anxiety symptom levels between participants with and without AD treatment

A two-way ANCOVA was run, controlling for age as a covariate, anxiety as a DV, and antidepressant treatment (AD users vs. non-users) and duration of depression (0-4 years vs. 5 or more years) as IV. The main effect of antidepressant treatment on anxiety levels did not reach the level of statistical significance, $F(1,305) = 3.48$, $p = .063$, $\eta_p^2 = .011$, but the mean anxiety symptom level was higher in non-users. No significant main effect of depression duration (0-4 years vs ≥5 years) on anxiety levels were found, $F(1,305) = .23$, $p = .635$, $\eta_p^2 = .001$. No statistically significant interaction between antidepressant treatment and duration of depression on anxiety levels was found, $F(1,305) = 1.80$, $p = .18$, $\eta_p^2 = .006$. However, a significant main effect of the covariate age was found, $F(1,305) = 8.82$, $p < .003$, $\eta_p^2 = .028$, as older age was associated with lower anxiety. The results are shown in Figure 1.

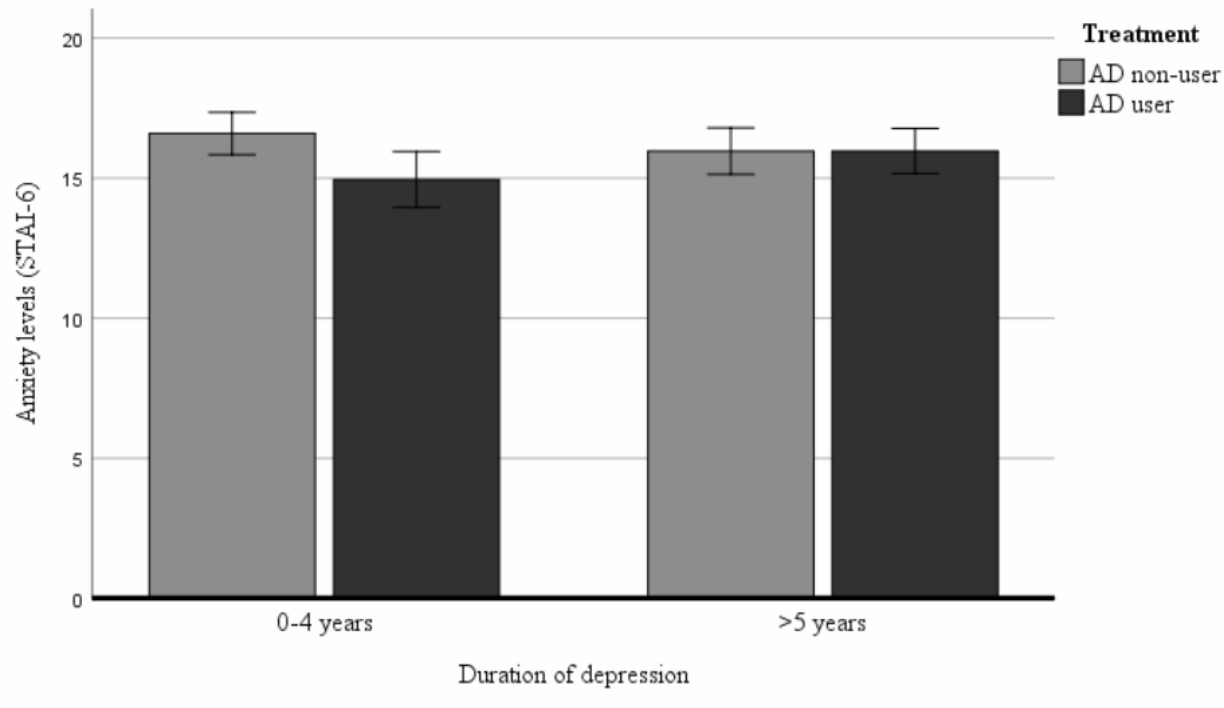

Figure 1. Anxiety levels of AD users (n = 137) vs. AD non-users (n = 189) with different durations of depression and age as a covariate. Error bars represent confidence intervals (95%).

As the group which was under antidepressant treatment was significantly older than the group not under antidepressant treatment, a follow-up analysis was run to control for the age confound. When excluding older (<30 years) participants, the difference in age between the AD users (n = 70, *M* = 16,09, *SD* = 3.70) and non-users (n = 162, *M* = 16.77, *SD* = 3.06) was no longer statistically significant, $t(230) = -1.65$, $p = .099$, $d = 0.20$. A 2 x 2 ANOVA was carried out with again anxiety as the DV, and duration of depression and antidepressant treatment as IVs. No main effect of antidepressant treatment was found, $F(1,204) = 2.33$, $p = .128$, $\eta_p^2 = .011$ and the interaction between antidepressant treatment and depression duration was also not significant, $F(1,204) = 3.29$, $p = .071$, $\eta_p^2 = .016$. However the main effect of depression duration reached the level of statistical significance , $F(1,204) = 3.93$, $p = .049$, $\eta_p^2 = .019$, as the mean anxiety level was slightly higher in those with longer depression duration (*M* = 16.93, *SD* = 3.35) than those with shorter depression duration (*M* = 15.94, *SD* = 3.28). This is graphically depicted in Figure 2.

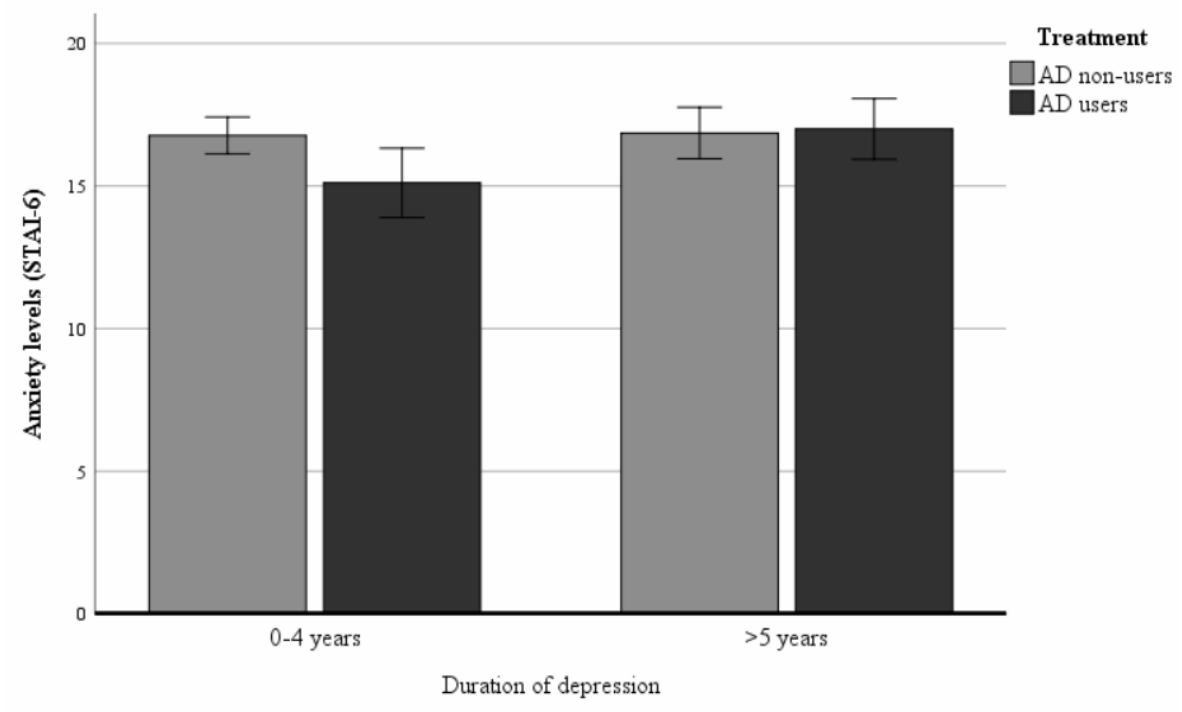

Figure 2. Anxiety levels in AD users (n = 70) vs. AD non-users (n = 162) under the age of 30 as a function of depression duration. Error bars represent confidence intervals (95%).

Gender could not be included as a between-groups factor in the main analysis due to very unequal group sizes, but a one-way between-subjects ANOVA was conducted to examine possible difference between the groups (women, men, transgender, other). No statistically significant difference was found, $F(3,380) = .59$, $p = .62$, although the mean STAI-6-value was highest for the transgender group ($M = 17.00$, $SD = 3.10$), and men ($M = 16.38$, $SD = 3.50$) had a higher anxiety symptom mean than women ($M = 15.99$, $SD = 3.44$).

3.2 Do anxiety symptom levels predict perceived side-effects of AD treatment?

Investigating the cohort under AD treatment, a previous factor analytic study in the DETRECO data by Sjöberg (2017) found that the side effects cluster into four factors (see more in "Instrument"). These factors, with acceptable levels of Cronbach's alpha, were labelled as "Estrangement" (α = .71), "Sexual side effects" (α = .84), "Dependency/Abstinence" (α = .67), and "Physical side effects" (α = .53). However, due to an earlier coding error, the physical side effects factor was missing a considerable amount of responses on the item "restlessness". This item was therefore removed in the current study. The items for each factor can be found in Table 2.

Since the sample size had increased after the study by Sjöberg was conducted, a new reliability analysis on the factor mean scores was conducted with the final DETRECO sample completed in 2017. The reliability of the factor mean scores was now even more satisfactory than in the original study: Estrangement α = .92, Sexual side effects α = .95, Dependency/Abstinence α = .91, and the new Physical side effects factor α = .89. Spearman's rho correlation tests were run for age, depression severity (QIDS-SR) and anxiety levels (STAI-6) with each side effect factor. These can be found in Table 3.

Table 2
Items Found in Each Side Effect Factor

Factor	Item
Estrangement (α = .92)	*"I care less about others"*
	"I don't feel like myself"
	"Aggression"
Sexual side effects (α = .95)	*"Anorgasmia"*
	"Sexual difficulties"
Dependency/Abstinence (α = .91)	*"Dependency on AD"*
	"Abstinence symptoms"
Physical side effects (α = .89)	*"Trembling"*
	"Dizziness"
	"Dry mouth"

Note. The items were responded to on a scale from 1 (*Not at all*) to 4 (*A lot*).

Table 3
Side Effects and Their Correlations with Anxiety and Age in Individuals under Antidepressant Treatment

	Age			QIDS-SR			STAI-6		
Factors	n	r_s	*p*	n	r_s	*p*	n	r_s	*p*
Estrangement	135	.023	.793	134†	.399	**.001**	135	.199	**.021**
Sexual	135	.152	.079	134	-.011	.90	135	-.228	**.008**
Dep./Abs.	125††	.191	**.032**	125	.123	.172	125	.035	.698
Physical	135	.054	.538	134	.293	**.001**	135	.119	.168

Note. Correlations of side effect factor with age, STAI-points (anxiety levels) and QIDS-SR (depression severity). Dep./Abs. = Dependency/Abstinence.
Bold = significant correlations.
†missing data due to respondents not completing QIDS-SR, ††missing data due to respondents not completing questions on dependency/abstinence items.

Several hierarchical multiple regressions were conducted, one for each side effect factor. Every analysis had two stages, with the side effect factor as the DV. Age and depression severity (QIDS-SR) were entered at stage one and anxiety level was entered at stage two of the regression. The variables were entered in this order as it was assumed that the physiology of ageing affects the metabolism of pharmaceuticals, and depression severity needs to be controlled for before exploring anxiety as it was the variable of interest.

In the estrangement side effect factor, the hierarchical multiple regression revealed that at stage one, age and depression severity contributed significantly to the regression model as a block, $F(2,131) = 11.30$, $p < .001$. However, it was the depression severity alone in this block which contributed significantly, accounting for 14.7% of the variation of estrangement side effects. Introducing the anxiety variable in step two explained an additional 0.1% of the variance in this side effect, but no significance as a block. These regression statistics are reported in Table 4.

In sexual side effects, the hierarchical multiple regression did not reveal any significant contribution of age and depression severity in the first step. However, when introducing the anxiety variable in step two, a significant contribution of anxiety on the variance was revealed, $F(3,130) = 3.52$, $p = .017$, accounting for 6.6% of the variance in sexual side effects. The relationship was negative, suggesting that the more sexual side effects experienced, the less anxiety experienced. This can be found reported in Table 5.

In the dependency/abstinence side effects factor no variable significantly contributed to the variance. Find this in Table 6.

Lastly, in the case of the physical side effects factor, the hierarchical multiple regression revealed that at stage one, age and depression severity contributed significantly to the regression model as a block, $F(2,131) = 7.81$, $p < .001$. However, it was again the depression severity alone in this block which contributed significantly, accounting for 9.3% of the variation. The regression statistics are reported in Table 7.

Table 4
Hierarchical Multiple Regression Analysis for Variables Predicting Estrangement Side Effects Factor

Variable	β	*t*	sr^2	R	R^2	ΔR^2
Step 1				.384**	.147	.147
Age	.093	1.151	.010			
QIDS-SR	.379	4.684**	.144			
Step 2				.385	.148	.001
Age	.098	1.192	.011			
QIDS-SR	.362	3.890**	.104			
STAI-6	.036	.382	.001			

Note: n = 134, sr^2 = semi-partial correlation squared, ΔR^2 = R square change.
*$p < .01$. **$p < .001$.

Table 5
Hierarchical Multiple Regression Analysis for Variables Predicting Sexual Side Effects Factor

Variable	β	*t*	sr^2	R	R^2	ΔR^2
Step 1				.093	.009	.009
Age	.087	1.00	.008			
QIDS-SR	.038	.438	.001			
Step 2				.274*	.075	.067
Age	.045	.520	.002			
QIDS-SR	.178	1.852	.026			

STAI-6	-.298	-3.058*	.067

Note: n = 134, sr^2 = semi-partial correlation squared, ΔR^2 = R square change.

*p < .01. **p < .001.

Table 6

Hierarchical Multiple Regression Analysis for Variables Predicting Dependency/Abstinence Side Effects Factor

Variable	β	*t*	sr^2	R	R^2	ΔR^2
Step 1				.199	.039	.039
Age	.124	1.398	.016			
QIDS-SR	.155	1.743	.024			
Step 2				.204	.042	.002
Age	.132	1.466	.016			
QIDS-SR	.127	1.247	.013			
STAI-6	.056	.540	.002			

Note: n = 134, sr^2 = semi-partial correlation squared, ΔR^2 = R square change.

*p < .01. **p < .001.

Table 7

Hierarchical Multiple Regression Analysis for Variables Predicting Physical Side Effects Factor

Variable	β	*t*	sr^2	R	R^2	ΔR^2
Step 1				.326**	.107	.107
Age	.079	.955	.007			

QIDS-SR	.323	3.902**	.104			
Step 2				.329	.108	.002
Age	.073	.864	.003			
QIDS-SR	.345	3.651**	.100			
STAI-6	-.046	-.478	.002			

Note: n = 134, sr^2 = semi-partial correlation squared, ΔR^2 = R square change.
*$p < .01$. **$p < .001$.

Discussion

The present study sought to first elucidate the association between antidepressant treatment and anxiety symptoms. It was expected that anxiety symptoms levels would be higher in AD non-users compared to AD users. The study did also aim to investigate possible associations between anxiety symptoms and AD side effects. Based on limited previous studies, higher levels of anxiety symptoms were expected to be associated with more severe AD side effects.

4.1 Anxiety, antidepressants, and age

In this data from the DETRECO project, a trend level difference in anxiety levels was found between AD users and AD non-users, but the effect was confounded by age, as AD-users were significantly older than the non-users. Age was, in fact, the only variable that had a statistically significant effect on anxiety symptoms, as older participants (irrespective of AD use) reported lower levels of anxiety symptoms. Secondary follow-up analyses which included only participants under the age of 30, hence matching the AD users and non-users at group level for age, showed no main effect of treatment on anxiety symptoms. Thus, the expected results of participants with AD treatment having significantly lower anxiety levels than those not using ADs was not found.

One possible explanation for the discrepancy between the results in the present study and those of previous studies is that anxiolytic effects may be specific to some ADs (Graeff

& Zangrossi, 2010; Lyndon et al., 2019). In the present study all AD-users were pooled together, irrespective of the specific type of AD, while both earlier studies by Nelson et al. (2005) and Cha et al. (2018) examined the effects of specific ADs. As various ADs have shown to have different effects on anxiety, and not controlling for type might have evened out the anxiolytic effects in the current study. SSRIs have been found to have a better response rate than bupropion for depressed patients with anxiety (Papakostas et al., 2008). Certain types of ADs are even approved for the treatment of anxiety disorders. Venlafaxine extended-release has shown efficacy for anxiety disorder (Rickels, Pollack, Sheehan & Haskins, 2000; Davidson, DuPont, Hedges & Haskins, 1999) and has been approved for the treatment of generalised anxiety disorder, social anxiety disorder and panic disorder, when comorbid with depression (Effexor XR [package insert], 2017 as cited in Lyndon et al., 2019). On the other hand, some types of ADs have been suggested to have the opposite effect (e.g. Baldwin et al., 2005; Toni et al., 2000).

The lack of a group effect of AD use on anxiety symptoms may also be due to not controlling anxiety levels reported with a cut-off point and possibly dividing participants into e.g. high anxiety and low anxiety groups in the current study. Previous studies have shown that anxiolytic effects of some ADs may be more likely to be present in those with very high anxiety levels. The previous study by Lyndon et al., (2019) suggested that depressed patients with higher anxiety levels had a significantly greater reduction of anxiety symptoms compared to those with low levels of anxiety. Therefore, in the current study a larger portion of participants may have had milder anxiety symptoms and thus an association between anxiety and AD-use might have been more difficult to find.

In the present study, almost half of the AD users reported polypharmacy, i.e. having at least one other psychotropic medication (often another type of antidepressant or a benzodiazepine); a common phenomenon in AD users (Dold et al., 2018; Kukreja, Kalra, Shah & Shrivastava, 2013). The effect of polypharmacy would, however, be more likely to reduce than increase the anxiety levels in the AD users groups. Benzodiazepines (and antipsychotics) are often used for their anxiolytic and sedative effects and thus it seems unlikely that polypharmacy would explain the lack of a difference in anxiety levels between AD users and non-users.

Another possible reason for differing results is that most studies showing anxiolytic effects of AD have been short-term studies (6-8 weeks), while long-term use currently, in fact, is the norm (Bet et al., 2013; Ferguson, 2001). In the present study, 43% had used AD

for 5 years or more, thus it is possible that anxiolytic effects may decrease with longer usage which perhaps gives an insight to anxiety levels changes in a naturalistic setting.

Age was a significant covariate in the main analysis in the current study; older age was associated with lower levels of anxiety. Anxiety decreasing with age has frequently been found in other studies. In personality research, a very high correlation between one of the big five traits, neuroticism, and anxiety has been found (Twenge, 2000, as cited in Twenge, 2000.). Neuroticism has consistently been found to decrease with age (McCrae et al., 1999; Srivastava, John, Gosling & Potter, 2003), with an evident decrease in almost every year of life (Scollon & Diener, 2006). In a recent study by Jensen, Kirkegaard, O'Connor and Mehlsen (2019), when older participants were asked to describe chapters and memories of their lives, they described them in a more positive light and scored lower on neuroticism compared to both young and middle-aged participants. Age was the strongest predictor for neuroticism which also enhanced their subjective well-being. There are also suggestions of a reduction of intrinsic susceptibility to anxiety and depression in association with ageing, which might be related to increased emotional regulation and so called psychological immunization to stressful experiences (Jorm, 2000). The fact that anxiety typically lessens as one gets older would be useful to communicate during treatment to young people suffering from anxiety. Psychoeducation about anxiety to patients formally diagnosed with anxiety disorders improved the quality of life and decreased psychological distress over time (Rodrigues, Bártolo, Pacheco, Pereira, Silva & Oliveira, 2018). Thus patients under AD-treatment should also be informed about the decreased prevalence of anxiety with ageing and what cognitive mindsets to practice.

On another note, although the number of participants reporting as transgender or "other" was very low, and statistical comparisons could not reliably be conducted, it should be noted that people identifying as transgender in the current sample reported very high levels of anxiety. Although the relatively low prevalence of transgender individuals has likewise kept samples small in other studies (Bouman, Claes, Brewin, Crawford, Millet & Arcelus, 2016), similar findings have been reported. A study on 913 individuals self-identified as transgender, found that they had an almost threefold risk of developing an anxiety disorder compared to the general population. Anxiety was associated with low self-esteem and interpersonal functioning. Similarly, higher levels of anxiety in transgender samples in comparison to the general population have been found in a systematic review in 2016 (Millet, Longworth & Arcelus, 2016).

The gender distribution in the present study was not balanced, thus limiting the analysis of gender differences, and in contrast with the previous studies, men reported higher levels of anxiety than women. According to the OECD (2018), anxiety, depressive and bipolar disorder are more common amongst women. In studies, women are often found to have significantly more anxiety symptoms (Gao, Ping & Liu, 2020) and/or be more prone to anxious depression (Fava et al., 2006), compared to men. However, there are studies which have found contrasting results where men might manifest more (e.g. Kalsoom, 2020) or as much (e.g. Peterson, Newton & Feingold, 2007) anxiety as women when both are in a more vulnerable health condition.

The significant difference in age between AD users and non-users was unfortunate as this made it impossible to entangle the effects of age and depression duration on anxiety in the two groups. Duration of depression naturally correlates with age as a younger individual will simply not have had the time to be depressed for the same amount of time as an older individual. However, a long-term study followed 49 patients diagnosed with depression over 25 years. After 25 years, only 12% had recovered and remained in remission, while 84% had recurrent episodes of depression, 2% had unremitting depression and 2% had committed suicide. Thus, the authors concluded that at least severe depression seemed to have poor long-term outcomes and also the older the individuals were, the longer they had been depressed (Brodaty, Luscombe, Peisah & Anstey, 2001).

4.2 Side effects of AD treatment and anxiety levels

The second aim of the study was to explore the association between side effects and anxiety levels, using side effects factors stemming from Sjöberg (2017). Contrary to expectations, higher anxiety levels were not associated with more severe side effects in any of the four side effects factors studied: Estrangement, Sexual, Dependence/Abstinence or Physical side effects. Rather counterintuitively, lower anxiety was related to more severe sexual side effects. There are various possible explanations for this finding. Sexual dysfunction and anxiety symptoms are generally two of the top priorities to avoid when prescribing AD (Zimmerman et al., 2004). However that does not mean that they are mutually prioritised and it could be that clinicians end up prioritizing one over the other, as both might not be easy to meet. Sexual side effects have also been suggested to be frequently ignored. Both clinicians and patients in Asia regard sexual side effects as a “forbidden topic” (Chen et al., 2008, p. E57), and spontaneous reporting of sexual dysfunctions are less

frequent also according to studies in Western societies (Ottosson, 2018). When overtly and directly assessed, sexual side effects are reported 55% of the time, whereas when left spontaneous to report by patient, it decreases to 2-7% (Ferguson, 2001).

A possible explanation is that anxiety might lead to lower sexual activity and sexual side effects might thus be left undiscovered. According to Barlow's model (1986), it is hypothesized that anxiety distracts attention from erotic cues and in turn reduces or impedes the sexual arousal or sexual activity in general. And Wolpe (1958, as cited in Kane, Dawson, Shaughnessy, Reissing, Ouimet & Ashbaugh, 2019) proposed that sexual arousal and anxiety might be mutually inhibitory as they are of opposing nervous system activations. Sexual arousal being activated by parasympathetic activation and anxious arousal by sympathetic activation. Likewise, social anxiety has been suggested to have a negative correlation with the amount of sexual contact, in women (but not in men; Kashdan, Adams, Savostyanova, Ferssizidis, McKnight & Nezlek, 2011), thus potentially decreasing sexual contact and in turn, decreasing the likelihood of experiencing sexual side effects. Nonetheless, recognition and patients' education of both anxiety and sexual side effects are imperative, and caution should be taken when describing ADs when earlier issues with sexual side effects are known.

Although not a focus in the current study, depression severity in the current sample predicted both estrangement and physical side effects. This is in line with earlier studies mentioned (Fava et al., 2008; Ionescu et al., 2014; Shankman et al.,2017), the greater depression severity, the more side effects are suggested to be experienced. The number of side effects is argued to increase with higher depression severity. Bet et al., (2013) conducted a naturalistic study on a large cohort of patients with depression and/or anxiety disorders. They found that on average, 2.9 side effects were reported in 64% of the patients in long-term AD treatment. Physical side effects have earlier also been suggested to relate to depression severity as depressed patients might have a higher attentiveness to physical discomfort (Bet et al., 2013 & Klauenberg et al., 2008)

Neither age, depression severity nor anxiety was related to dependency/abstinence side effects. Nevertheless, to properly examine these variables would require that respondents have at some point tried to stop or be remitted from AD treatment (Fava et al., 2015). Yet, the respondents who were not currently under AD treatment, but had been in the past, were omitted from the current sample. And therefore, valuable data for these side effects might have been lost with them. Thus, an extension of this study looking into that cohort could be worth investigating.

Despite earlier studies finding anxiety symptoms having a detrimental and increasing effect on AD treatment side effects, the current study did not find supporting results. Nonetheless, lesser sexual side effects were found with higher anxiety symptom levels which is intriguing and calls for more controlled studies.

4.3 Strengths and limitations

The strength of this study is mainly the relatively large dataset from the DETRECO project which allowed wide explorations of demographic, clinical variables and relationships of a big Finnish sample. Being able to utilise the data and complement Sjöberg's (2017) study with even higher reliability in data, is also a potential strength. It is suggested that there is limited literature on AD treatment in older cohorts as they are excluded due to presence of confounding comorbidities or concomitant medication (Mittman et al., 1997), and instead, treatment recommendations are often extrapolated from younger patients. The current study included respondents up to 63 years old and therefore, making an important contribution to the literature.

There are also several limitations to the current study. The study used a convenience sample which entails a significant risk of selection bias. The sample may not be representative of the population of people suffering from depression. Since usage of AD treatment has previously been shown to be very frequent, it puts doubt on the representability of the current sample as the majority were not AD users. Moreover, for analysing effects of AD on anxiety levels a placebo-controlled randomized trial would be the gold standard, although these trials can typically only examine effects over the short term (6-8 weeks). Examining effects over the long term can typically only be conducted using naturalistic follow-up designs. Also, the study had a cross-sectional design, while a longitudinal design would allow for examining changes in anxiety levels over time in both AD users and non-users.

A female majority, with four times more females than men in the sample might have affected the results. Some side effects such as weight gain have been found to be associated with the female gender (Bet et al., 2013) even though weight change was not a side effect investigated in the present study.

The low number of items in the STAI-6 assessment forced a summation of the anxiety measure in the current study. The potential of extracting specific information from the individual items was lost (e.g. "*I feel calm*" vs. "*I feel nervous*") and might be a limitation of

the study. However, the summation gave the analysis higher reliability and more power. Another potential limitation to the utilisation of STAI-6 is that there are currently no studies, at least known to the author, which has investigated the cut-off points for clinical anxiety or generally expected anxiety level of healthy controls when using STAI-6. Thus, if all the current studies participants' anxiety levels were not at a clinical level, perhaps seeing differences between the AD users and non-users would not have been possible anyway.

Another limitation to the data was the earlier coding error of the side effect of "*restlessness*" which required omittance of this item from the physical side effect factor.

Using self-report also has some weaknesses which entails among others, the issues of social desirability, comprehension of questions posed (Del Boca & Noll, 2000; Kwon et al., 2003), sampling bias etc. Moreover, since this was a sample of potentially depressed individuals there might have been a higher risk of fatigue and incompletion of questionnaires. Those who did not complete the survey might have been respondents with the highest depression severity (Luyten, Kempke, Van Wambeke, Claes, Blatt & Van Housenhove, 2011). Moderate to severe depression has been found in 70% of patients diagnosed with chronic fatigue syndrome (Walker, Lindner & Noonan, 2009). Therefore, to decrease the risk of missing out on these respondents, making self-reports as short and concise as possible for this particular population might be something to consider for future studies.

4.4 Future research and implications

The current study can be extended by matching the groups of AD-users and non-users on factors such as age and gender in a randomised trial with a longitudinal design. In this way, state-anxiety differences could be investigated in a more controlled study allowing examination of potential changes in anxiety levels over time. Moreover, the current study utilises correlational statistical analysis in examining anxiety levels and AD-use vs. non-use. However, comparing groups, e.g. low- and high-anxiety, could be more fruitful and has been done in earlier studies by Ionescu et al., (2014) and Fava et al., (2008). It would also be interesting to investigate possible differences between those solely using an antidepressant compared to those using more psychotropic treatments (polypharmacy).

The present study could be further extended by investigating sexual side effects and its negative relationship with anxiety levels more in detail. Earlier hypotheses point in two different directions (Kane et al., 2019) of anxiety increasing or decreasing sexual activity and

response. And since sexual side effects and anxiety are two of the most considered side effects in AD choice, a better insight would support or reject the current widespread practice.

Two other aspects worth examining is within the interplay of age and AD treatment. One is examining the efficiency of AD treatment in different age cohorts, and investigating possible factors which might associate with experienced anxiety and AD treatment. The other aspect could be examining subjective motivation of patients of different ages in using AD treatment and how that could be related to subjective anxiety. Nevertheless, the current study leaves questions unanswered between the age difference of those using and not using AD medication. And since there is a greater paucity of research into older samples, a more controlled and clinically valid examination of this cohort should be sought after.

The findings of the current study could be applied to the clinical setting when choosing treatment and/or psychoeducation for people suffering from depression and anxiety. The present study suggests that AD, in general, might not be associated with lower or higher anxiety levels. Lower anxiety seems to be related to more experienced sexual side effects of AD. Therefore, anxiety symptom levels and sexual dysfunctions should be considered in clinical guidelines for the treatment of depression, but also adapted in the choice of AD treatment, at least when it comes to side effects. Patients should also receive psychoeducation on the association between increasing age and lower anxiety. Moreover, greater patient informed consent and clinicians' recognition of anxiety symptoms and sexual side effects should be sought after and caution in the prescription of AD should be warranted (Andrews et al., 2012).

4.5 Conclusion

The present study did not find a difference in anxiety levels between depressed individuals under antidepressant treatment vs. those not under antidepressant treatment. Instead, age was found to correlate with anxiety levels which already has wide support in the literature. Previous studies showing anxiety alleviating effects of AD have mostly been short-term clinical trials. Possible anxiolytic effects of AD in long-term use thus clearly needs to be studied with more controlled designs. The current study did also find that depressed respondents who were under AD treatment were more likely to experience sexual side effects if their anxiety levels were low. This is counterintuitive and calls for more research inquiring about this relationship. It was also found that anxiety levels do not relate to other side effects, in contrast with earlier suggestions of anxiety worsening the experience of side effects.

However, the side effects of dependency/abstinence might require more research and include those respondents who have experience of AD treatment but have now gone off them. Conclusively, as anxiety and sexual side effects have earlier shown effects on clients' well-being and choice of antidepressants, the current study suggests that attention and raising awareness to these factors are crucial in clinician's' choice of treatment of depression.

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Summary in Swedish - Svensk Sammanfattning

Ångestsymtom i depression: är de relaterade till antidepressiva läkemedel och läkemedlens biverkningar?

Depression är en av världens vanligaste psykiska sjukdomar, vilket påverkade ungefär 264 miljoner människor år 2017 (GDB Disease and Injury Incidence and Prevalence Collaborators, 2017). Depression har även varit den vanligaste anledningen till psykisk ohälsa i Finland de senaste decennierna (The Organisation of Economic Co-operation and Development, 2018; OECD). Enligt den femte upplagan av Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) är depressionssymtom bl.a. nedstämdhet, anhedoni, aptit- och sömnstörningar, kognitiv nedsättning och känslor av hopplöshet. Ofta känner personer med depression även ångest (Montgomery, 2019), vilket verkar vara komorbid med depression hos upp till 78% av befolkningen som har depression (Gaspersz, Nawijn, Lamers & Penninx, 2018).

Den vanligaste behandlingen för depression i världen och Finland är antidepressiva (AD) läkemedel (Honkonen, Aro, Isometsä, Virtanen & Katila, 2007; National Institute for Health and Clinical Excellence, 2004). Selektiva hämmare av serotoninåterupptag (SSRIs) är den vanligaste typen av AD (Ottosson, 2018). Långtidsanvändningen av AD (över fem år) har ökat sedan 1994 både i världen (Lockhart & Guthrie, 2011; Moore et al., 2009) och i Finland (Sihvo et al., 2010). Forskning stöder även effektiviteten av antidepressiva hos patienter med depression och ångest (e.g. Lyndon, Prieto, Wajsbrot, Allgulander & Bandelow, 2019). Trots ADs popularitet är det vanligt att biverkningar uppstår vid AD-behandling (Ottosson, 2018) vilket försvåras när depression ackompanjeras av ångest (Ionsescu, Niciu, Richards & Zarate, 2014). Syftet med denna avhandling är att närmare undersöka ångestsymtom i depression och om ångestsymtom varierar beroende på AD-behandling. Även en undersökning av potentiella associationer mellan ångestsymtom och biverkningar av AD utförs.

Ångestsymtom (state-anxiety) definieras som den subjektiva upplevelsen av ett stort hot mot ens person. Den uppstår som en reaktion av ett resultat av anlag för ångest och stressiga omständigheter. Anlag för ångest i denna mening syftar på den ångest som även finns som en del av vår personlighet (trait-anxiety; Derakshan & Eysenck, 2009; Eysenck, 1992). Det förstnämnda ångestsymtomet präglas av starka känslor av oro och rädsla och är den sortens ångest som är i fokus i denna studie. Mellan 42-80% av vuxna med depression har ångestsymtom på klinisk nivå (Gaspersz et al., 2018; Lyche, Jonassen, Stiles, Ulleberg &

Landrø, 2010; Zimmerman et al., 2000) men ofta utesluts dessa patienter från urval i kliniska studier just på grund av svårigheterna med att studera patienter med denna komorbiditet (Zimmerman, McDermus & Mattia, 2000).

Depression med ångestsymtom har påvisats vara svårbehandlat (Gaspersz et al., 2018) och vara associerat med högre risk för självmord (Allgulander, 2000, as cited in Lyndon et al., 2019). Jämfört med patienter med endast depression har patienter med komorbid ångestsymtom svårare depression, högre depression kronicitet, större psykosociala utmaningar, ökad risk för återfall (Altamura, Montresor, Salvadori & Mundo, 2004; Fava et al., 2006; Lyche et al., 2010; Weiss et al., 2016; Wiethoff et al., 2010) och minskad livskvalitet (Gaspersz et al., 2018; Ionescu et al., 2013).

Antidepressiva läkemedel hävdas också ha ångestdämpande effekter (Ottosson, 2018). En metaanalys av randomiserade placebo-studier fann en signifikant minskning av ångestsymtom efter AD-behandling (Nelson, Portera & Leon, 2005). En studie av Cha et al. (2018) jämförde deprimerade personer som fick AD-behandling med en kontrollgrupp som inte var deprimerad. Cha och hens kollegors resultat visade att ångesten hos de deprimerade var signifikant mycket lägre efter AD-behandling jämfört med kontrollgruppen. Ytterligare en metaanalys av Lyndon et al. (2019) undersökte patienter med depression där de delades in i antingen låg eller hög ångestsymtom innan AD-behandling (6-12 veckor). De fann två positiva utfall: (1) både den låga och höga ångest-gruppen hade signifikant mindre ångest än placebo och (2) gruppen med hög ångest hade signifikant större lindring i ångest än gruppen med låg ångest.

Det finns dock nackdelar med AD-behandling då flera olika sorters biverkningar har rapporterats. Fysiska biverkningar inkluderar abstinensbesvär, sexuella dysfunktioner och viktökning (Cartwright, Gibson, Read, Cowan & Denhar, 2016). Kognitiva biverkningar inkluderar utmattning, minnesproblem och koncentrationssvårigheter (Popovic et al., 2015). Andra biverkningar från en studie i Nya Zeeland på långtidsanvändande av AD hos 1829 vuxna rapporterade minskning i positiva känslor, likgiltighet till andra och självmordstankar (Read, Cartwright & Gibson, 2014). Dessa biverkningar kan förvärras när ångestsymtom är närvarande i depression (Fava et al., 2008; Ionescu et al., 2014) men det finns begränsat med studier inom detta fält då forskare har tenderat att fokusera på ångeststörningar istället för endast ångestsymtom (Hung et al., 2020).

En annan eventuell nackdel med AD-behandling är att vissa forskare hävdar att det finns en publiceringsbias som resulterat i en överskattning av AD-behandlingen effektivitet och en underskattning av dess biverkningar. Detta förklaras oftast vara relaterat till finansiella

anledningar då många kliniska studier är sponsrade av läkemedelsindustrin (Ebrahim et al., 2016; Fava et al., 2016). De studier som finns publicerade kritiseras för att bara undersöka korttidsanvändning (6-8 veckor) av AD som sällan kan appliceras till verklighetens norm av AD-användning (Bet et al., 2013; Ferguson, 2001). Utgivarna av studier kritiseras även för att generellt publicera studier som inte använder tillräckligt objektiva mätinstrument för undersökning av biverkningar i AD (Gartlehner et al., 2008).

Studiens syfte

Syftet med denna studie var att utforska associationen mellan ångestsymtom och antidepressiv behandling. Den första målsättningen var att undersöka AD-behandlingens påverkan på ångestsymtom. I tidigare studie av Cha et al. (2018) mättes ångestsymtom under AD-behandling men studien jämförde deprimerade med friska personer och saknade en deprimerad grupp som inte var på AD-behandling. Denna studie söker att fylla detta tillkortakommande genom att jämföra ångestsymtom hos deprimerade individer som behandlas eller inte behandlas med AD-behandling. Baserat på tidigare forskning (t.ex. Lyndon et al., 2019; Nelson et al., 2005) förväntas deprimerade individer uppleva mindre ångestsymtom efter AD-behandling än deprimerade individer som inte genomgått AD-behandling.

Den andra målsättningen var att undersöka associationen mellan ångestsymtom och biverkningar från AD-behandling. Baserat på tidigare begränsad forskning förväntas det att biverkningar upplevs i högre grad ju mer ångestsymtom individen upplever (Fava et al., 2008; Ionescu et al., 2014). Specifikt i denna studie förväntas det att inom AD-gruppen upplevas mer biverkningar ju högre ångestsymtom som upplevs.

Metod

Datainsamlingen var en del av ett större projekt vid Åbo Akademi vid namnet Depressionsbehandling och kognitiva funktioner (DETRECO). Med godkännande från Åbo Akademis etiska granskningsnämnd, pågick insamlingen av enkäter mellan år 2015-2017. Det primära syftet med DETRECO var att undersöka depression och kognitiva funktioner.

Denna studie hade initialt 386 individer. Några respondenter (n = 60) indikerade att de tidigare använt AD men inte gör det längre. Dessa togs bort för att få en mer kontrollerad studie. Studien hade då 326 personer i samplet indelat i två grupper: en grupp aktuella i en AD-behandling (AD-grupp; n = 137) och en grupp som aldrig varit med i en sådan

behandling (icke-AD-grupp; n = 189). Samplet bestod av 65 män, 250 kvinnor, 5 transpersoner och 6 som identifierade sig som "annat", alla inkluderades i huvudanalysen. Kön analyserades senare som en dikotom variabel (man/kvinna) vilket fann att AD och icke-AD-gruppen skildes sig signifikant i kön, $\chi 2(1, N = 315) = 5.96$, $p = .015$. Kvinnor var en aning överrepresenterade i AD-gruppen (81%) i jämförelse med icke-AD-gruppen (73%). Grupperna skilde sig även signifikant i ålder då samplet var mellan 18-63 år gamla (M = 28.66, SD = 9.02). AD-gruppen (M = 32.74, SD = 10.63) var signifikant äldre än icke-AD-gruppen (M = 25.70, SD = 6.17), $t(201.92) = -6.96$, $p < .001$, $d = 0.81$. Det fanns en skillnad på depressionskronicitet där depression ofta varade längre (≥ 5 år) hos AD-gruppen, $\chi^2(1\ N = 311) = 20.18$, $p < .001$. Likväl fanns inga skillnader mellan grupperna gällande utbildningsnivå, $t(324) = .75$, $p = .457$, $d = 0.09$, eller depressionssvårighet (QIDS-SR), $t(377) = -.537$, $p = .592$, $d = 0.002$. Polyfarmaci var också relativt vanligt. 45% av AD-användare rapporterade minst en psykoaktiv medicinering.

Rekryteringen genomfördes som ett bekvämlighetsurval. Deltagare i enkäterna rekryterades med hjälp av marknadsföring på olika vårdinstanser i Finland, internt genom annonser på Åbo Akademi, på Studenthälsan i Åbo och genom sociala medier (t.ex. Facebook). Studien gjordes online på en testplattform, SOILE, utvecklad av Brain Train Research Centre of Excellence på Institutionen av Humaniora, Psykologi och Teologi vid Åbo Akademi. Hela DETRECO-projektet innehöll en finskspråkig och omfattande depressionsrelaterad undersökning och arbetsminnestest. För att delta i undersökningen förutsätts en subjektiv upplevelse av depressionssymtom eller en diagnos av depression.

Tre självskattningsformulär från projektet har analyserats i denna studie. Den första var Quick Inventory of Depressive Symptomatology 16 items (QIDS-SR(16); Rush et al., 2003; Appendix A) som ämnar att mäta depressionens svårighet. Det andra skattningsformuläret var en kortare version av state-ångest enkäten Spielberger State-trait Anxiety Inventory (STAI-6; Marteau & Bekker, 1992; Appendix B). Den tredje skattningen undersökte både positiva och negativa fysiska och psykiska biverkningar (Read, Cartwright and Gibson, 2014; Appendix C). En explorativ faktoranalys av dessa biverkningar från DETRECO projektet hade redan gjorts av Sjöberg (2017) där undersökningen av potentiella underliggande faktorer och medelvärden gjordes. Baserat på Cronbach's Alpha hade fyra faktorer av biverkningar tillräckligt god reliabilitet. Dessa faktorer var senare analyserade och utvecklade i denna studie. Mer information om faktoranalysen finns att hitta i Sjöberg (2017). Fler frågor som användes från projektet var frågor om depressionens längd (kronicitet) och användning av AD läkemedel.

Den statistiska analysen genomfördes med IBM SPSS Statistics 26.0 för Windows (IBM Corp., 2019). Alla analyser hade alpha nivå på p <.05. För att analysera ångestsymtom i AD och icke-AD-gruppen utfördes en 2 x 2 ANCOVA. Effekter av AD-behandling (ja/nej) och depression kronicitet (</> 5 år) var oberoende variabler (OBV) medan ångestsymtom var den beroende variabeln (BV). Ålder fungerade som kovariat för att kontrollera för eventuella ovidkommande faktorer då det fanns en signifikant skillnad på ålder mellan grupperna. Man förväntade sig en huvudeffekt av AD-behandling där AD-gruppen skulle rapportera lägre nivåer av ångestsymtom än icke-AD-gruppen. Analysen upprepas en andra gång med ett subsample av deltagare som var 30 år och yngre.

Det andra syftet med studien analyserades med hjälp av multipel hierarkisk regressionsanalys på alla fyra biverknings-faktorer: Utanförskap, Sexuella, Beroende/Abstinens och Fysiska biverkningar. Här undersöktes endast den gruppen som var aktuell med AD-behandling (n = 137). Ångestsymtom var återigen BV som prediceras av de ovan fyra biverkningar som fungerade som OBVs, baserade på Sjöbergs (2017) studie från DETRECO-projektet. I första steget inkluderades ålder och depressionssvårighet (QIDS-SR) som två prediktorer, medan i andra steget infördes ångestsymtom (STAI-6) som en tredje prediktor. Andra faktorer som kontrollerades för var kön och utbildningsnivå. Det förväntades att ångestsymtom nivåer skulle vara associerade med upplevda biverkningar, vilket innebar ju högre ångestsymtom desto högre nivå av biverkningar.

Resultat

Skillnader i ångestsymtom nivåer hos deltagare med och utan AD-behandling

En 2 x 2 ANCOVA med ålder som kovariat, ångest som BV, och AD-behandling (AD-användning vs. icke-AD användning) och depression kronicitet (0-4 år vs. ≥ 5 år) som OBV genomfördes. En huvudeffekt av AD-behandling på ångestnivåer uppnådde inte statistisk signifikans, F(1,305) = 3.48, p = .063, ηp2 = .011, men medelvärdet av ångestsymtom var högre i icke-AD-gruppen. Depressions kronicitet (0-4 år vs ≥5 år) hade inte heller en huvudeffekt på ångest, $F(1,305) = .23$, $p = .635$, $\eta_p^2 = .001$. Som förväntat fanns ingen interaktion mellan AD-behandling och depressions kronicitet, $F(1,305) = 1.80$, $p = .18$, $\eta_p^2 = .006$. Dock visade resultaten att ålder var en signifikant huvudeffekt, $F(1,305) = 8.82$, $p < .003$, $\eta_p^2 = .028$.

Eftersom AD-gruppen var signifikant äldre än icke-AD-gruppen, kördes en kontroll univariat 2 x 2 ANOVA på endast deltagare som var upp till 30 år. Återigen hittades inte någon huvudeffekt av AD-behandling, $F(1,204) = 2.33$, $p = .128$, $\eta_p^2 = .011$, depression kronicitet, $F(1,204) = 3.93$, $p = .049$, $\eta_p^2 = .019$, eller interaktion mellan kronicitet och AD-behandling, $F(1,204) = 3.29$, $p = .071$, $\eta_p^2 = .016$.

På grund av den obalanserade fördelningen av kön i de två grupperna avstod vi från att använda kön som en mellangruppsvariabel i huvudanalysen. Istället genomfördes en inspektion av eventuella skillnader i ångestsymtom mellan de olika grupperna (kvinna, man, transperson,"annan"). Ingen signifikant statistisk skillnad hittades, $F(3,380) = .59$, $p = .62$. Däremot är det värt att nämna att ångest var högst hos transpersoner ($M = 17.00$, $SD = 3.10$), medan män ($M = 16.38$, $SD = 3.50$) hade högre ångest än kvinnor ($M = 15.99$, $SD = 3.44$).

Predicerar ångestsymtom upplevda biverkningar i AD-behandling?

För att inspektera biverkningar hos AD-gruppen användes tidigare resultat från Sjöberg (2017). Sjöberg fann fyra biverkningsfaktorer som med det kompletta samplet från 2017 fick ännu högre Cronbach's Alpha-nivåer. Dessa blev kategoriserade som "Utanförskap" ($\alpha = .92$), "Sexuella biverkningar" ($\alpha = .95$), "Beroende/Abstinens" ($\alpha = .91$) och "Fysiska biverkningar" ($\alpha = .89$). Det bör nämnas att på grund av ett tidigare kodningsfel saknade Fysiska biverkningar omfattande data på frågan om "rastlöshet". Detta item togs därför bort från faktorn i denna studie.

En multipel hierarkisk regressionsanalys genomfördes för varje biverkningsfaktor. I utanförskapsklustret avslöjades vid steg ett att ålder och depressionssvårighet som ett block bidrog signifikant till regressionen, $F(2,131) = 11.30$, $p < .001$. Det var dock depressionssvårighet som ensam variabel signifikant predicerade 14.7% av variationen i utanförskapsklustret. När analysen sedan introducerade ångest i steg två, fanns ingen signifikant varians från ångest som block.

Inom sexuella biverkningar fann multipel hierarkisk regressionsanalysen inga signifikanta prediktorer från ålder och depressionssvårighet i något av blocken. När ångest introducerades i steg två däremot, indikerade resultaten att ångest predicerade 6.6% av variansen, $F(3,130) = 3.52$, $p = .017$. Relationen var negativ vilket föreslår att ju mer sexuella biverkningar som upplevs, desto mindre ångestsymtom upplevs.

I analysen av fysiska biverkningar presenterades ålder och depressionssvårighet som signifikanta bidrag till variansen som ett block i steg ett, $F(2,131) = 7.81$, $p < .001$. Men

återigen är det depressionssvårigheter som ensam faktor predicerar 9.3% av variansen i fysiska biverkningar. Det fanns inga signifikanta prediktorer i biverkningsfaktorn beroende/abstinens.

Diskussion

Denna avhandling hade som syfte att undersöka associationer mellan antidepressiv behandling och ångestsymtom. Första syftet var att utvärdera om ångestsymtom är lägre hos de som har AD-behandling än hos de som inte har AD-behandling. Det andra syftet var att undersöka om ångestsymtom ökade risken att uppleva högre nivåer av biverkningar från AD-behandling.

Ångest, antidepressiv behandling och ålder

Från data tagen från DETRECO-projektet fann denna avhandling en skillnad i ångestsymtom nivåer mellan de som hade AD-behandling och de som inte hade det. Dock var denna trend påverkad av ålder då AD-gruppen var äldre än icke-AD-gruppen. Ålder var den enda signifikanta huvudeffekt på ångestsymtom och ju äldre individerna blev ju mindre ångestsymtom verkade upplevas. Trots sekundära analyser med ålders-matchning där endast deltagare som var högst 30 år inkluderades fanns ingen huvudeffekt av AD-behandling (AD-användning vs. icke-AD användning).

Avhandlingens resultat är i motstridighet till tidigare forskning av t.ex. Nelson et al. (2005) och Cha et al. (2018). Det dessa studier gjorde annorlunda var att kontrollera för typen av AD som användes av deltagarna. Det finns även tidigare forskning som föreslår att vissa AD läkemedel har ångestdämpande effekt (Graeff & Zangrossi, 2010; Lyndon et al., 2019), medan andra har den motsatta effekten (e.g. Baldwin et al., 2005; Toni et al., 2000). Detta kan ha resulterat i att de båda effekterna slog ut varandra i den aktuella studien.

Svårigheter i att hitta skillnader i ångestsymtom mellan användare och icke-användare av AD kan också ha berott på det specifika samplet i denna avhandling. Många av deltagarna använde flera antidepressiva läkemedel, så kallad polyfarmaci. Detta är relativt vanligt (Kukreja, Kalra, Shah & Shrivastava, 2013) och deprimerade patienter verkar använda i medelvärde 2.18 psykotropiska läkemedel per person (Dold et al., 2018). Samplet kan även ha haft en generellt lägre ångestnivå. Lyndon et al. (2019) hävdade att ångestdämpande effekter är tydligare när deprimerade patienter har hög ångestsymtom. En stor andel av samplet (43%) hade även varit under AD-behandling i fem år eller mer, vilket kan ha minskat ångesten med tiden. Tidigare studier på AD och dess ångestdämpande effektivitet har varit

korttidsstudier (6-8 veckor) trots att långtidsanvändning är normen (Bet et al., 2013; Ferguson, 2001).

Resultaten indikerade att ångestsymtom minskade med ålder. Detta är inte överraskade då inom forskningen kring personlighet och femfaktormodellen har man hittat höga korrelationer mellan ångest och neuroticism (Twenge, 2000, as cited in Twenge, 2000). Och det finns tydligt forskningsstöd i att neuroticism minskar med åren (McCrae et al., 1999; Srivastava, John, Gosling & Potter, 2003).

Trots icke signifikanta resultat upplevde transpersoner mer ångest än resten av samplet överlag, samt männen upplevde mer ångest än kvinnorna. I linje med tidigare forskning utgör transpersoner sällan en stor del av ett sampel inom litteraturen men har eventuellt tre gånger så stor risk att lida av ångest än den allmänna populationen. Män brukar oftast uppleva mindre ångest än kvinnor (Fava et al., 2006; Gao, Ping & Liu, 2020) men det finns studier som visar att män kanske upplever lika mycket eller mer ångest när de finner sig i en sårbar situation som en mentalsjukdom (e.g. Kalsoom, 2020; Peterson, Newton & Feingold, 2007).

Biverkningar och ångestsymtom

Inga biverkningar ökade i samband med ångestsymtom, men ångest ledde till högre risk för sexuella biverkningar och vice versa. En potentiell förklaring är att både ångest och sexuella biverkningar är de två högst prioriterade faktorerna i klinikers val av AD läkemedel (Zimmerman et al., 2004) vilket kan betyda att ena väljs över den andra när man väljer vilken som ska undvikas, eller så är det svårt att prioritera båda samtidigt. Det finns även studier som menar att sexuell dysfunktion ofta ignoreras när man frågar klienter om deras biverkningar (Chen et al., 2008).

Ångest kan ibland leda till mindre sexuell aktivitet vilket gör att sexuella biverkningar då lämnas oupptäckta. Enligt Barlows modell (1986) skulle ångest distrahera uppmärksamheten från erotiska signaler och då minska sexuell upphetsning och sexuell aktivitet. Social fobi har eventuellt en negativ korrelation med frekvensen av sexuell kontakt med andra och på det sättet minskar det potentiella situationer där sexuella biverkningar av AD-behandling kan upplevas.

Depressionssvårighet predicerade både utanförskap och fysiska biverkningar och är i linje med tidigare nämnda studier om att ju svårare depressionen är desto mer biverkningar kan upplevs. En ökning av fysiska biverkningar är kanske inte heller så överraskade då

deprimerade klienter kan ha en förhöjd uppmärksamhet och upplevelse av fysiska besvär (Bet et al., 2013 & Klauenberg et al., 2008).

Det bör även nämnas att beroende/abstinensbiverkningar inte predicerades av någon av variablerna ålder, depressionssvårighet eller AD-behandling. Detta kan ha varit på grund av att en relativ stor grupp av deltagare i enkäten togs bort för att de inte var aktuella med AD-behandling men hade genomgått en innan. Eftersom beroende och abstinens förutsätter försök att avsluta AD-behandling kan studien förlorar värdefull information från denna grupp som exkluderades.

Styrkor och Svagheter

Styrkor i denna avhandling är den omfattade datainsamlingen från DETRECO-projektet, dess breda finska population samt tillgången till Sjöbergs (2017) tidigare faktoranalys för att sedan få en ännu starkare reliabilitet i biverkningsfaktorer för denna studie. En ytterligare styrka i avhandlingen är att den även undersöker äldre klienter där tidigare litteratur oftast tagit bort dessa deltagare på grund av att de har högre risk för komorbiditet.

Denna avhandling har även några begränsningar. De största svagheterna var kanske studiens bekvämlighetsurval och att det var en tvärsnittsstudie vilket utgör en signifikant risk för urvalsfel och mindre representativ sampel. En optimal undersökning av AD-behandling skulle vara en placebo-kontrollerad och randomiserad studie. Dock kan dessa oftast bara vara korttidsinterventioner och och långtidsbehandling är oftast bara möjliga att undersöka i naturalistiska miljöer.

En annan begränsning är att samplet har en fyra gånger större del kvinnor än män. Vissa biverkningar som förändringar i vikt ska exempelvis vara mer associerat med det kvinnliga könet (Bet et al., 2013). Till andra begränsningar hör det att det låga antalet items i STAI-6 tvingade en summering av ångestskalan istället för en analys av varje item. På det sättet förlorade studien eventuell specifik information om ångest. En annan svaghet är nackdelarna med självskattning. Samplet var av en klinisk deprimerad kohort vilket kan spekuleras att de deltagare som inte deltog eller inte fyllde i hela enkäten kan ha varit dem som lider av den svåraste graden av depression och i sin tur bli utmattade snabbare (Luyten, Kempke, Van Wambeke, Claes, Blatt & Van Housenhove, 2011). Därför bör framtida forskning av speciellt deprimerad population ta undersökningens längd och användarvänlighet i beaktande.

Framtida forskning, tillämpning och sammanfattning

Framtida forskning skulle kunna fortsätta undersöka AD-behandling hos urvalsgrupper som är matchade i ålder och kön samt kontrollera för användning av specifika typer eller antal AD-läkemedel. I enlighet med tidigare studier av t.ex. Ionescu et al., (2014) and Fava et al., (2008) skulle grupperna även kunna delas upp i låg och hög ångest. På detta sätt kan ångestsymtom studeras över tid i en mer kontrollerad design.

Den aktuella studien kan även expanderas genom i mer detalj inspektera sexuella biverkningar och dess negativa korrelation med ångestsymtom. Oklara hypoteser om ångest och sexuella drifter behöver förtydligas i empiriska studier. Fynden från denna avhandling skulle även kunna bidra i det kliniska området då val av typ av behandling för depression sker. Om AD-behandling skulle vara aktuellt bör klienten informeras om dess biverkningar, få tydlig och bred psykoedukation om AD-behandling och läkemedlet bör anpassas efter klientens symtom-bakgrund.

Sammanfattningsvis är depression en psykisk sjukdom som påverkar många människor världen över. Fler som drabbas av depression upplever även ångestsymtom. Antidepressiva läkemedel är den mest prevalenta behandlingen för depression men i denna avhandling fanns det inga skillnader på ångestnivåer hos dem som hade eller inte hade genomgått AD-behandling, istället var ålder en faktor som associerades med ångestsymtom. Vidare minskar sexuella biverkningar från AD-behandling hos den deprimerade individen ju högre ångest hen får. Detta är kontraintuitivt och en djupare dykning i detta förhållande skulle vara intressant i framtida forskning. Beroende och abstinens biverkningar blev eventuellt inte rättvist undersökt i denna studie och kan behövas uppmärksammas igen. Den aktuella studien påvisar ett behov av att ge klienter tydligare och kanske mer omfattande informerat samtycke och psykoedukation inom AD-behandlingens effektivitet i ångestdämpning och dess biverkningar.

Appendix A

Quick Inventory of Depressive Symptomatology (QIDS SR-16)

Tick the one response to each item that best describes you for the past seven days.

1. Falling Asleep:

a. I never take longer than 30 minutes to fall asleep.
b. I take at least 30 minutes to fall asleep, less than half the time.
c. I take at least 30 minutes to fall asleep, more than half the time.
d. I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:

a. I do not wake up at night.
b. I have a restless, light sleep waking up briefly a few times each night.
c. I wake up at least once a night, but I go back to sleep easily.
d. I wake up more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

a. Most of the time, I wake up no more than 30 minutes before I need to get up.
b. More than half the time, I wake up more than 30 minutes before I need to get up.
c. I almost always wake up at least one hour or so before I need to get up, but I go back to sleep eventually.
d. I wake up at least one hour before I need to get up, and cannot go back to sleep.

4. Sleeping Too Much:

a. I sleep no more than 7-8 hours/night, without napping during the day.
b. I sleep no more than 10 hours in a 24-hour period including naps.
c. I sleep no more than 12 hours in a 24-hour period including naps.
d. I sleep more than 12 hours in a 24-hour period including naps.

5. Feeling Sad:

a. I do not feel sad.
b. I feel sad less than half the time.
c. I feel sad more than half the time days.
d. I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

a. There is no change in my usual appetite.
b. I eat somewhat less often or lesser amounts of food than usual
c. I eat much less than usual and only with personal effort.
d. I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

7. Increased Appetite:

a. There is no change from my usual appetite.
b. I feel a need to eat more frequently than usual.

c. I regularly eat more often and/or larger amounts of food than usual.
d. I feel driven to overeat both at mealtimes and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (Within the Last 14 Days)

a. I have not had a change in my weight.
b. I feel as if I have had a slight weight loss.
c. I have lost 1kg or more. d. I have lost 2kg or more.

9. Increased Weight (Within the Last 14 Days)

a. I have not had a change in my weight.
b. I feel as if I have had a slight weight gain.
c. I have gained 1 kg or more.
d. I have gained 2 kg or more

10. Concentration/Decision Making:

a. There is no change in my usual capacity to concentrate or make decisions.
b. I occasionally feel in decisive o find that my attention wanders.
c. Most of the time I struggle to focus my attention or to make decisions.
d. I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

a. I see myself as equally worthwhile and deserving as other people.
b. I am more self-blaming than usual.
c. I largely believe that I cause problems for others.
d. I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

a. I do not think of suicide or death.
b. I feel that life is empty or wonder if it is worth living.
c. I think of suicide or death several times over the past 7 days for several minutes.
d. I think of suicide or death several times a day in some detail or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest:

a. There is no change from usual in how interested I am in other people or activities.
b. I notice that I am less interested in people or activities.
c. I find I have interest in only one or two of my formerly pursued activities.
d. I have virtually no interest in formerly pursued activities.

14. Energy Level:

a. There is no change in my usual level of energy.
b. I get tired more easily than usual.
c. I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
d. I really cannot carry out most of my usual daily activities because I just don’t have the energy.

15. Feeling More Sluggish Than Usual:

a. I think, speak, and move at my usual rate of speed.

b. I find that my thinking is more sluggish than usual or that my voice sounds dull or flat.

c. It takes me several seconds to respond to most questions and I am sure my thinking is more sluggish than usual.

d. I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

a. I do not feel restless.

b. I'm often fidgety, wringing my hands, or need to shift around when I am sitting.

c. I have impulses to move about and am quite restless.

d. At times, I am unable to stay seated and need to pace around.

Appendix B

State-Trait Anxiety Inventory (STAI-6)

1. I feel calm

a. Not at all
b. Somewhat
c. Quite a lot
d. A lot

2. I feel nervous

a. Not at all
b. Somewhat
c. Quite a lot
d. A lot

3. I feel upset

a. Not at all
b. Somewhat
c. Quite a lot
d. A lot

4. I feel relaxed

a. Not at all
b. Somewhat
c. Quite a lot
d. A lot

5. I feel satisfied

a. Not at all
b. Somewhat
c. Quite a lot
d. A lot

6. I feel worried

a. Not at all
b. Somewhat
c. Quite a lot
d. A lot

Appendix C

Perceived side effects of AD treatment developed by Read, Cartwright and Gibson (2014)

Estimate to what extent you have perceived following side effects from the antidepressant medication:

Nausea
a. Not at all
b. Some
c. Moderate
d. A lot

Diarrhea
a. Not at all
b. Some
c. Moderate
d. A lot

Headache
a. Not at all
b. Some
c. Moderate
d. A lot

Sexual difficulties
a. Not at all
b. Some
c. Moderate
d. A lot

Anorgasmia
a. Not at all
b. Some
c. Moderate
d. A lot

Suicidal thoughts
a. Not at all
b. Some
c. Moderate

Dependency on antidepressants
a. Not at all
b. Some
c. Moderate
d. A lot

Dry mouth
a. Not at all
b. Some
c. Moderate
d. A lot

Sleepiness
a. Not at all
b. Some
c. Moderate
d. A lot

Dizziness
a. Not at all
b. Some
c. Moderate
d. A lot

Gaining weight
a. Not at all
b. Some
c. Moderate
d. A lot

Losing weight
a. Not at all
b. Some
c. Moderate
d. A lot

Trembling
a. Not at all
b. Some
c. Moderate
d. A lot

I don't feel like myself
a. Not at all
b. Some
c. Moderate
d. A lot

Blunted emotions
a. Not at all
b. Some
c. Moderate
d. A lot

Less positive emotions
a. Not at all
b. Some
c. Moderate
d. A lot

Aggressiveness
a. Not at all
b. Some
c. Moderate
d. A lot

I care less of others
a. Not at all
b. Some
c. Moderate
d. A lot

d. A lot

Abstinence symptoms

a. Not at all
b. Some
c. Moderate
d. A lot

Restlessness

a. Not at all
b. Some
c. Moderate
d. A lot

If you have perceived other side effects: *Type them here*

Pressmeddelande

Antidepressiva läkemedel kan leda till ökad sexuella biverkningar vid låg ångest

Pro gradu-avhandling i Psykologi
Fakulteten för Humaniora, Psykologi och Teologi, Åbo Akademi

Resultaten från en pro gradu-avhandlingen vid Åbo Akademi fann att antidepressiva läkemedel kanske inte är så effektiva mot ångest. Sally Lo har undersökt deprimerade individers ångest, antidepressiva läkemedel och dess biverkningar inom ramen av projektet "DETRECO" på Åbo Akademi. Hon fann att antidepressiva läkemedel inte kunde kopplas till förändringar av ångest hos användare. I studien jämfördes ångesten hos deprimerade individer som använder antidepressiva läkemedel, med deprimerade individer som inte använder antidepressiva läkemedel. De som använde antidepressiva var inte mindre ångestfyllda än de utan läkemedlet. Det bör dock nämnas att det finns olika sorters antidepressiva, men som en grupp fungerade antidepressiva inte som ångestdämpare.

Enligt Los studie har de individer som hade lägre ångest fler sexuella biverkningar, jämfört med dem som hade högre ångest och mindre sexuella biverkningar. Dessa biverkningar var svårigheter i att uppnå orgasm trots stimulation och andra sexuella svårigheter.

Enligt Lo är detta fynd viktiga för klinikers arbete då de bör beakta patienters sexuella biverkningar och ångest till en längre utsträckning än idag. Kliniker bör var noga med att informera sina patienter om antidepressivas effektivitet i ångest och dess biverkningar. Samtidigt bör även patienter vara tydliga med biverkningar och andra symptom de upplever under depressionen.

Sammanlagt deltog 326 deprimerade individer i studien, varav 137 fick antidepressiv behandling och 189 fick det inte. Information samlades in online med hjälp av formulär som bland annat mätte ångest samt negativa och positiva upplevelser av antidepressiva biverkningar. Framtida studier rekommenderas att undersöka eventuella anledningar och förhållandet mellan ångest och sexuella biverkningar.

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