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Effect of severity of depression on augmentation of antidepressant medication in young adults with depression

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Abstract

Background: Antipsychotics (AP) have been used to augment antidepressant (AD) medication in treatment-resistant depression. In this study we examined factors (including severity of depression and initial antidepressant) affecting AP augmentation, as well as which APs were initiated as augmentation in young adults.

Methods: Data were extracted from Finnish nationwide registers. Of persons aged 18–29 years diagnosed with a depression during 2004–2017 we focused on incident AD users (who initiated AD 6 months before and after the diagnosis) whose severity level of depression was recorded ($N = 21{,}966$). AP augmentation was studied during 1 year after diagnosis of depression. Persons diagnosed with severe depression with psychotic features ($n = 1486$) were excluded from main analyses and analyzed separately.

Results: Overall, 8.4% of new antidepressant users initiated AP augmentation. Risk of augmentation increased with severity of depression as 3.9%, 5.8%, and 14.0% of persons with mild, moderate, and severe depression, respectively, initiated augmentation. Male sex, comorbid anxiety and personality disorders, substance abuse and selfharm/suicide attempt were positively associated with augmentation. Compared to citalopram, use of tricyclic antidepressant, paroxetine and venlafaxine were associated with increased risk of augmentation, while use of bupropion was associated with a decreased risk. Quetiapine and risperidone were the most common APs used in augmentation. Among persons with severe depression with psychotic features, use of sertraline was associated with AP augmentation, whereas use of fluoxetine decreased risk of augmentation.

Conclusions: Use of APs as augmentation of AD therapy was common in severe depression. Comorbidities had only a small effect to augmentation, but selection of initial AD was more closely associated to risk of augmentation. Interestingly, use of bupropion decreased risk of augmentation, which warrants further studies, as well as the decrease in risk of augmentation when fluoxetine in case of psychotic depression was used.

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KEYWORDS
antidepressants, antipsychotics, augmentation, depression, pharmacotherapy, young adults

1 | INTRODUCTION

Depressive disorders are one of the most common causes of disability worldwide in persons aged 10–49 years,[1] and, for example, in the United States, rates of major depressive disorder were in year 2017 up to 13.2% among young adults aged 18–25 years.[2] The treatment of depressive disorders is based on pharmacotherapy and psychotherapy. Often, antidepressant medication is initiated as first-line treatment. Most antidepressants target monoamine (especially serotonin or noradrenaline) neurotransmitter function, but their therapeutic effect may result also from, for example, changes in neural plasticity.[3,4] Different types of antidepressants include selective serotonin re-uptake inhibitors (SSRIs, e.g., citalopram), serotonin and noradrenaline reuptake inhibitors (SNRIs, e.g., venlafaxine), noradrenergic and specific serotonin antidepressants (NaSSAs, e.g., mirtazapine), tricyclic antidepressants (TCAs, e.g., amitriptyline) as well as monoamine oxidase inhibitors (MAOIs, e.g., selegiline).[5] In addition, novel antidepressants such as vortioxetine (multimodal action to serotonergic, noradrenergic and dopaminergic systems), bupropion (inhibitor of noradrenaline and dopamine reuptake) and agomelatine (melatonergic MT_1 and MT_2 agonist and 5-HT_{2C} antagonist) have presented somewhat different mechanisms of action compared to traditional antidepressants.[6,7] Generally, SSRIs are recommended as the first-line antidepressant.[8]

Despite an adequate therapeutic trial, up to two thirds of patients do not achieve remission, and up to 33% will fail to respond even after multiple interventions.[9] Treatment-resistant depression (TRD) is most frequently defined as failure to respond to two trials of pharmacological therapy of adequate dose and duration, in the current episode.[10] In these cases, antidepressant therapy may be augmented by combining with another type of antidepressant, mood stabilizers, ketamine, thyroid hormones and atypical antipsychotics. Among these, quetiapine, aripiprazole, brexpiprazole, olanzapine, ziprasidone, and risperidone have been used in augmentation.[11–13] Their effect is thought to arise at least partially from blockade of 5-$HT_{2A/2C}$ receptors, which may improve the efficacy and side effect profile of SSRIs.[14] On the other hand, atypical antipsychotics also have their side effects, including extrapyramidal symptoms, dyslipidemia, weight gain and increased prolactin levels,[15] so their use should be carefully considered.

Significant Outcomes

- Use of antipsychotics as augmentative agents increased with severity level of depression.
- Use of TCAs, paroxetine and venlafaxine were associated with antipsychotic augmentation, while bupropion was associated with decreased risk of augmentation in persons with depression without psychotic features.
- In persons with severe depression with psychotic features, use of sertraline was associated with AP augmentation, while use of fluoxetine was associated with decreased risk of augmentation.

Limitations

- We had no data about other therapies such as psychotherapy or neuromodulation therapies.
- Data is based on dispensed drugs but we have no information if some of these were not consumed.

Despite the fact that depression is common and AD treatment is commonly modified in young adults,[16] information about factors associated with AP augmentation is greatly limited. Zhou et al.[17] have recently published a study of 1503 patients with non-psychotic depression in adult population, but their study included only 834 persons aged 18–44 years. In this study, we have examined how often an antidepressant medication is augmented with antipsychotics among young adults (aged 18–29 years), and sociodemographic and clinical factors associated with augmentation.

2 | MATERIALS AND METHODS

The base cohort for this study included all persons diagnosed with depression (International Classification of Diseases ICD-10 F32-F33) at the age of 18–29 years during the years 2004–2017 ($N = 110{,}761$, representing 3.8% of the Finnish population aged 18–29 years; 2.5% men and 5.3% women). They were identified from nationwide Finnish registers: inpatient care and specialized

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outpatient care (the Care Register for Health Care, maintained by National Institute of Health and Welfare), sickness absence (maintained by Social Insurance Institution, SII) and disability pensions (identified from registers of SII and Finnish Centre for Pensions). Persons were chosen based on not having a diagnosis of bipolar disorder (F30-F31) or schizophrenia-spectrum disorder (F20-F29) before being diagnosed with depression. The Care Register for Health Care includes all visits to hospitals and specialized outpatient care. Sickness absences included sick leaves of ≥14 days. Sick leaves and disability pensions also included diagnoses from primary care. All registers are linkable with personal identity codes assigned for all residents.

2.1 | Study design

The study population was formed by determining initiations of antidepressants at earliest 6 months before the depression diagnosis was first given and at latest 6 months after the depression diagnosis. These treatment episodes were considered as most likely associated with the depression diagnosis, and acknowledged the fact that some persons had been treated in primary care before their first diagnosis was registered in our data sources. In this study, we restricted the study population to incident antidepressant users ($N = 52{,}855$, 47.7%), who initiated antidepressant use during the time period 6 months before to 6 months after the diagnosis and who had not used antidepressants during 6 months before the first initiation identified during the period (6 months washout). Thus, we excluded persons who were using antidepressants and not fulfilling incident user definition (e.g., having used during the washout period, prevalent users using antidepressant continuously) ($N = 21{,}620$, 19.5%), and also non-users ($N = 36{,}286$, 32.8%), who were those who did not have any antidepressant use during 6 months before and after the diagnosis. Then we also restricted to individuals for which their severity of depression was recorded at the diagnosis or during the following 180 days (i.e., fourth character of ICD-10 could be found in the register), $N = 21{,}966$. In addition, those who were diagnosed with severe depression with psychotic features (F32.3, F33.3, $N = 1486$) were excluded from primary analyses and analyzed separately, resulting in a study group of 20,478 persons.

2.2 | Exposure and outcomes

The Prescription register data on drug dispensings includes ATC-code, dispensed amount, date of dispensing, package size and strength. Drug dispensing data was converted to drug use periods with "From drug purchases to drug use periods" (PRE2DUP) method.[18] Drug use periods refer to estimates of when drug use started and ended based on dispensing dates, amounts dispensed and drug-specific parameters. The method also takes into account stockpiling, days spend in hospital care and personal regularity of use.

Antidepressants were defined as ATC category N06A, but excluding the smallest strength (15 mg) mirtazapine to distinguish mirtazapine used for depression from small dose mirtazapine, which is commonly prescribed for insomnia (in doses not effective for depression). For each incident user, we defined initial antidepressant as either monotherapy of any of the antidepressants, or as polytherapy which refers to initiation of two or more antidepressants at the same day. Initial antidepressants were further categorized as tricyclic antidepressants (TCA, N06AA), SSRIs (N06AB), mirtazapine (>15 mg), SNRIs (venlafaxine, duloxetine, milnacipran), and other antidepressants (moclobemide, mianserin, trazodone, bupropion, reboxetine, agomelatine, vortioxetine).

Augmentation with antipsychotics (N05A excluding lithium) was assessed after antidepressant initiation and within a time window of 6 months before and until 1 year after diagnosis. All antipsychotics were considered but quetiapine use was only considered when used ≥100 mg/day as also low dose quetiapine is often prescribed for insomnia (in doses not effective for depression augmentation). Augmentation was defined as >90 days concomitant use of antidepressant plus antipsychotic. Date of augmentation outcome was defined as start date of concomitant use which lasted >90 days. The 90 days period was chosen because medications can be dispensed for 3 months of treatment at a time. In these analyses, follow-up was censored to death, diagnoses of bipolar disorder/schizophrenia-spectrum disorder, and end of data linkage December 31, 2018.

2.3 | Covariates

Covariates were measured at the date of diagnoses (age), or at the date of antidepressant initiation (the rest of the covariates). Comorbid conditions were measured based on diagnoses recorded in the Care Register for Health Care, the Prescription register (Attention Deficit Hyperactivity Disorder [ADHD], diabetes) and by supplementing diagnosis data from Special Reimbursement register which includes data on granted special reimbursements for medications due to specific chronic conditions. Other medication use was measured during 6 months before antidepressant initiation based on Prescription register data modeled with PRE2DUP method. Detailed definitions of covariates are provided in Supplementary Table 1.

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Severity level of depression was used as a covariate and analyses were also stratified based on the severity level. Severity level was defined during the first 180 days after initial depression diagnosis as the highest level recorded during the time period if multiple levels were recorded. Severity was categorized as mild (F32.0, F33.0), moderate (F32.1, F33.1) versus severe (F32.2, F33.2), by excluding those who did not have any diagnosis recorded with the fourth digit level and those who had only been recorded with "other depressive episodes (F32.8, F33.8) or 'depressive episode', unspecified" (F32.9, F33.9).

2.4 | Analyses

Descriptive statistics were calculated with proportions and medians with interquartile ranges (IQRs). Factors associated with augmentation were assessed with Cox proportional hazard models, adjusting for all covariates. Persons with severe psychotic depression (F32.3, F33.3) were excluded from main analysis and analyzed separately. Statistical analyses were performed with SAS version 9.3 (SAS Institute, Inc., Cary, NC).

3 | RESULTS

From the study group (20,480 persons), 181 Severity level of depression 1 persons (8.8%) had mild depression, while depression was classified as moderate or severe on 11,703 (57.1%) and 6966 (34.0%) persons, respectively. Two thirds of them were female, and the share of younger age group increased with severity of depression (Table 1).

(Es)citalopram was the most common initial AD followed by sertraline, fluoxetine, venlafaxine and mirtazapine, regardless of the severity of depression. Baseline use of benzodiazepines and Z-drugs was more common among persons with severe depression compared to those with mild depression.

Of the study population, 1724 (8.4%) persons initiated AP augmentation. In general, age did not affect initiation of augmentation. Augmentation was infrequently initiated among persons with mild depression (3.9%), but the share increased with the severity level of depression (5.8% and 14.0% in persons with moderate and severe depression, respectively) (Table 1). Baseline characteristics of persons who did and did not initiate augmentation are shown in Table 2.

Men initiated AP augmentation more often than women (adjusted HR, 95% CI 1.40, 1.27–1.55). Severity of depression increased risk of AP augmentation (1.50, 1.17–1.92 and 3.48, 2.73–4.44 for moderate and severe depression, respectively, compared to mild depression). Previous hospital-treated depression was also associated with AP augmentation initiation (2.17, 1.92–2.44) (Figure 1).

Compared to citalopram, use of TCA (2.36, 1.54–3.61), paroxetine (1.50, 1.14–1.98), or venlafaxine (1.23, 1.02–1.47) were positively associated with AP augmentation. Conversely, use of bupropion decreased risk of augmentation (0.68, 0.47–0.98).

Among psychiatric comorbidities, substance abuse (1.32, 1.12–1.54), personality disorder (1.28, 1.05–1.55), and anxiety disorder (1.21, 1.09–1.34) were associated with AP augmentation, as well as baseline use of benzodiazepines and Z-drugs (1.61, 1.39–1.86 and 1.30, 1.12–1.52, respectively) (Figure 1).

When we focused on patients with moderate or severe depression, some differences emerged. Male sex and previous hospital-treated depression were associated with AP augmentation in both groups (Figure 2). In addition, anxiety (1.49, 1.27–1.75) and personality (1.39, 1.04–1.87) disorders were associated with AP augmentation among persons with moderate depression, and substance abuse among persons with severe depression (1.33, 1.07–1.66). Other psychiatric or somatic comorbidities were not associated with AP augmentation in severe depression. When considering initial antidepressants, only TCA was associated with AP augmentation in persons with moderate depression (3.23, 1.81–5.75), whereas use of duloxetine (1.52, 1.02–2.27) was associated with an increased risk of AP augmentation in persons suffering from severe depression. Use of benzodiazepines (1.62, 1.28–2.04 and 1.56, 1.30–1.89 for moderate and severe depression, respectively) and Z-drugs (1.37, 1.07–1.75 and 1.27, 1.04–1.55 for moderate and severe depression, respectively) was associated with AP augmentation in both groups.

The most commonly used antipsychotics for augmentation were quetiapine (39.6%), risperidone (19.7%) and olanzapine (17.9%) (Figure 3). Severity of depression was not associated to their use. Use of perphenazine (4.9%) and aripiprazole (3.3%) were less common, and their use focused on less severe forms of depression.

Those persons with diagnosis of severe depression with psychotic features (F32.3, F33.3, $N = 1486$) were analyzed separately, and the results are presented in Supplementary Table 2. Briefly, antidepressant therapy was augmented with APs in 806 persons (54.2%). Previous hospital-treated depression (1.65, 1.42–1.92) was associated with AP augmentation, whereas selfharm/suicide attempt (0.66, 0.49–0.90) was associated with decreased odds of AP augmentation. Choice of initial AD had only subtle effects to AP augmentation, as only sertraline (1.31, 1.02–1.68) was associated with augmentation, whereas use of fluoxetine (0.73, 0.54–0.99) was associated with decreased odds of AP augmentation.

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TABLE 1 Baseline characteristics by severity level of depression measured during the first 6 months after first diagnosis.

	Mild $N = 1811$	Moderate $N = 11{,}703$	Severe without psychotic features $N = 6966$
Age 18–24	65.6 (1188)	68.7 (8036)	70.9 (4940)
Age 25–29	34.4 (623)	31.3 (3667)	29.1 (2026)
Male sex	35.5 (643)	32.7 (3827)	34.8 (2427)
Previous AD use	25.2 (457)	26.2 (3063)	24.8 (1725)
Previous hospital-treated depression	6.0 (109)	8.9 (1043)	17.7 (1235)
Initial antidepressant			
Escitalopram	29.3 (531)	30.3 (3551)	30.7 (2140)
Citalopram	26.5 (480)	20.9 (2440)	18.8 (1308)
Mirtazapine	6.1 (110)	6.8 (795)	8.3 (579)
Sertraline	12.1 (219)	13.2 (1547)	11.4 (793)
Fluoxetine	8.4 (152)	10.6 (1243)	10.2 (709)
Venlafaxine	6.5 (117)	8.0 (936)	9.1 (631)
Paroxetine	2.8 (50)	2.3 (265)	2.1 (149)
Bupropion	2.4 (43)	2.2 (259)	2.9 (199)
Duloxetine	2.0 (37)	1.9 (218)	2.0 (139)
TCA	1.1 (19)	0.6 (70)	0.5 (33)
Other AD	2.9 (53)	3.2 (379)	4.1 (286)
Psychiatric comorbidities			
Anxiety disorder	29.7 (538)	27.4 (3202)	24.9 (1734)
Personality disorder	3.4 (61)	4.0 (464)	4.5 (316)
Eating disorder	5.2 (94)	4.6 (543)	4.2 (289)
Autism spectrum disorder	0.8 (15)	0.9 (105)	0.8 (56)
ADHD	2.2 (39)	2.4 (278)	1.9 (132)
Substance abuse	6.2 (113)	6.3 (734)	6.9 (481)
Selfharm/suicide attempt	1.7 (31)	2.7 (311)	4.5 (311)
Somatic comorbidities			
Cancer	4.0 (73)	4.6 (532)	4.3 (301)
Diabetes	2.7 (48)	2.3 (273)	2.2 (153)
Asthma	9.1 (165)	9.8 (1145)	9.5 (658)
Baseline drug use			
Benzodiazepines	6.9 (125)	7.3 (849)	8.8 (610)
Z-drugs	7.6 (138)	7.6 (884)	8.8 (616)
Initiates concomitant use	3.9 (70)	5.8 (680)	14.0 (974)

Abbreviations: AD, antidepressant; TCA, tricyclic antidepressant.

4 | DISCUSSION

As expected, augmentation of antidepressant medication with antipsychotics was uncommon in persons with mild or moderate depression. However, some AP initiations were noted, which may arise from, for example, need to improve patient's sleep or stem from comorbidities such as substance abuse or personality disorders. Among persons suffering from severe depression, 14.0% initiated antipsychotic augmentation. Zhou et al.[17] have recently reported slightly higher results, as in their study AP augmentation was initiated to 179 of 834 (21.5%) young adults (18–44 years) with major depressive disorder.

In the initiation of AD medication, severity of depression had only small effect on the choice of drug, as use of mirtazapine and venlafaxine (which both increase

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TABLE 2 Baseline characteristics compared between those who initiated antipsychotic augmentation versus those who did not initiate.

	No augmentation $N = 18{,}756$	AP augmentation $N = 1724$	Unadjusted HR (95% CI)
Age 18–24	69.3 (12,989)	68.2 (1175)	0.95 (0.86–1.05)
Age 25–29	30.8 (5767)	31.8 (549)	Ref.
Male sex	32.9 (6179)	41.7 (718)	1.45 (1.31–1.59)
Severity level of depression			
Mild	9.3 (1741)	4.1 (70)	Ref.
Moderate	58.8 (11,023)	39.4 (680)	1.52 (1.19–1.94)
Severe without psychotic features	32.0 (5992)	56.5 (974)	3.83 (3.01–4.88)
Previous AD use	25.2 (4725)	30.2 (520)	1.27 (1.14–1.40)
Previous hospital-treated depression	10.4 (1956)	25.0 (431)	2.94 (2.63–3.27)
Initial antidepressant			
Escitalopram	30.7 (5756)	27.0 (466)	0.98 (0.85–1.13)
Citalopram	20.8 (3902)	18.9 (326)	ref
Mirtazapine	7.2 (1344)	8.1 (140)	1.27 (1.04–1.55)
Sertraline	12.4 (2324)	13.6 (235)	1.23 (1.04–1.46)
Fluoxetine	10.4 (1946)	9.2 (158)	0.96 (0.80–1.17)
Venlafaxine	8.0 (1501)	10.6 (183)	1.47 (1.23–1.76)
Paroxetine	2.2 (405)	3.4 (59)	1.68 (1.27–2.21)
Bupropion	2.5 (470)	1.8 (31)	0.84 (0.58–1.22)
Duloxetine	1.9 (359)	2.0 (35)	1.17 (0.83–1.66)
TCA	0.5 (99)	1.3 (23)	2.60 (1.70–3.96)
Other AD	3.5 (650)	3.9 (68)	1.31 (1.01–1.70)
Psychiatric comorbidities			
Anxiety disorder	26.3 (4932)	31.4 (542)	1.31 (1.19–1.46)
Personality disorder	3.8 (720)	7.0 (121)	1.94 (1.61–2.33)
Eating disorder	4.5 (851)	4.4 (75)	0.98 (0.78–1.24)
ADHD	0.8 (152)	1.4 (24)	1.15 (0.85–1.56)
Substance abuse	2.2 (406)	2.5 (43)	1.92 (1.65–2.23)
Selfharm/suicide attempt	6.1 (1139)	11.0 (189)	1.66 (1.33–2.07)
Somatic comorbidities			
Diabetes	3.0 (570)	4.8 (83)	0.93 (0.67–1.29)
Asthma	2.3 (437)	2.2 (37)	1.05 (0.90–1.23)
Baseline drug use	9.6 (1795)	10.0 (173)	
Benzodiazepines	7.3 (1364)	12.8 (220)	1.81 (1.57–2.09)
Z-drugs	7.7 (1448)	11.0 (190)	1.45 (1.25–1.69)

Abbreviations: AD, antidepressant; TCA, tricyclic antidepressant.

serotonin- and noradrenaline neurotransmission) slightly increased with severity of depression. There were no major differences in the use of SSRIs. Previously it has been suggested that SNRIs may be more effective than SSRIs for severe depression, but there is controversy.[19,20]

Being male increased the risk of AP augmentation. This may be due to underdiagnosis of depression in men due to the lower tendency of men to seek help,[21] which likely results in men having a more severe stage of depression than women at the time of diagnosis. AP augmentation risk was increased also among those who had had inpatient care due to depression suggesting a more complex situation.

Comorbidities had some effect on augmentation risk, as reported also by Zhou et al.[17] In our study, personality

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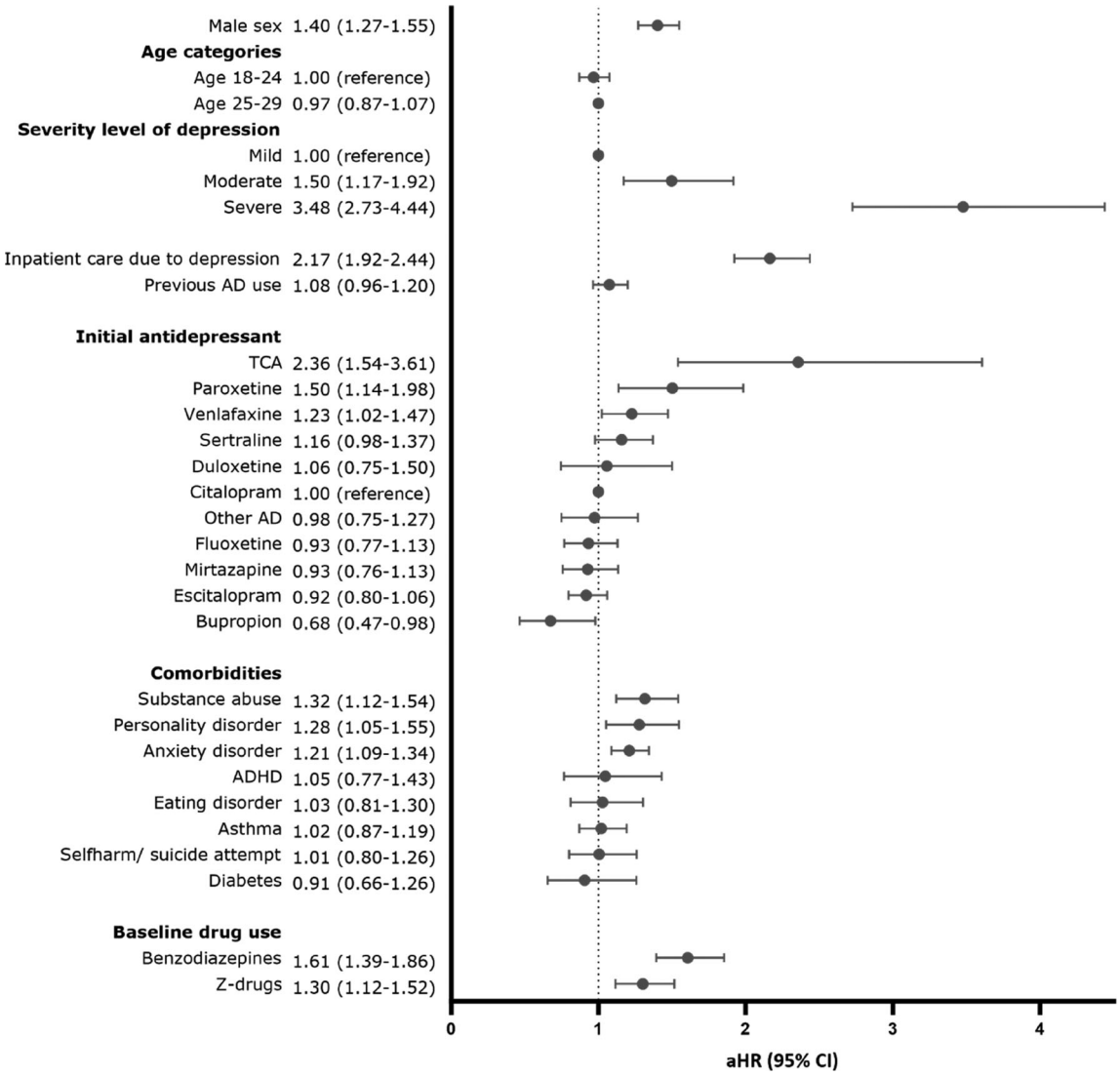

FIGURE 1 Factors associated with initiation of antipsychotic augmentation, adjusted hazard ratios (aHRs) from Cox regression model. Adjusted for all factors listed in the figure.

and anxiety disorders and substance abuse slightly increased the risk. It is interesting, that anxiety disorder increased the risk only in persons with moderate depression but not in severe depression. It is possible, that persons with severe depression and anxiety disorder may have had, for example, psychotherapy in addition to medication more frequently than those having "only" moderate depression in addition to anxiety disorder. Unfortunately, we do not have data on additional therapies.

The choice of initial antidepressant affected the risk of augmentation. Use of TCA was associated with highest risk of augmentation, followed by paroxetine and venlafaxine. Of these, initiation with venlafaxine increased with severity of depression, which may explain its association with augmentation. However, this does not apply to TCA (which was used mainly in mild depression) or paroxetine (in which severity of depression had no effect). In the meta-analysis by Qin et al.,[22] fluoxetine was more effective than paroxetine and TCAs in the treatment of children, adolescents and young adults. These results are in accordance with our results. Selection of TCA as an initial antidepressant may arise also from, for example, need to treat comorbid neuropathic pain[23] in addition to depression.

On the other hand, use of bupropion as an initial AD decreased the risk of augmentation in severe depression. Bupropion was used slightly more often in severe (2.6%) than in mild (2.4%) or moderate (2.2%) depression, so this is unlikely to explain decreased augmentation risk. Bupropion is an atypical antidepressant inhibiting the reuptake of dopamine and noradrenaline. In general, it has been found to be equally as effective in depression as the SSRIs and other antidepressants,[24–26] although

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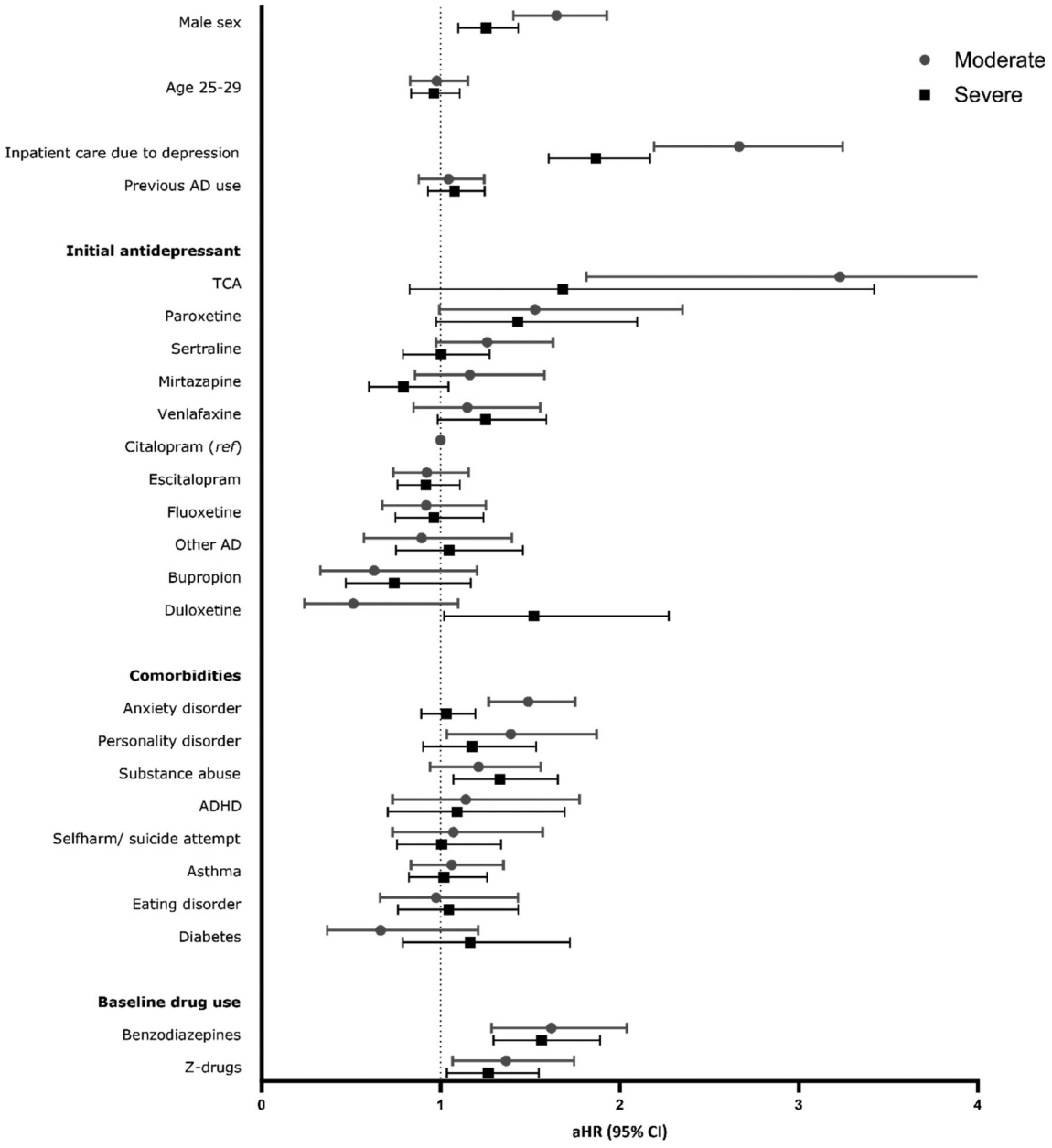

FIGURE 2 Factors associated with initiation of antipsychotic augmentation stratified by baseline severity of moderate versus severe depression, adjusted hazard ratios (aHRs) from Cox regression model. Adjusted for all factors listed in the figure.

there are also reports suggesting that SSRI may be slightly more effective than bupropion in suicidal depression at the initiation phase[27] or in patients with anxious depression.[28] On the other hand, bupropion has showed greater improvement in sleepiness and fatigue compared to SSRIs.[29] In addition, a recent systematic review presented some data suggesting that bupropion may be less associated to antidepressant-induced apathy than, for example, SSRIs.[30] Sexual dysfunction is also a markedly less common side-effect of bupropion compared to SSRIs.[31] These factors may contribute to the finding.

In our study, the use of benzodiazepines increased AP augmentation risk. The association of continued concomitant use of antidepressant and benzodiazepine to poorer depressive outcomes has previously been reported, being most likely due to GABA downregulation, decrease in monoaminergic function and neurogenesis, and negative effects on cognition.[32]

Atypical antipsychotics (quetiapine, risperidone, olanzapine and aripiprazole) were the most commonly used augmentative agents in our study population, as other antipsychotics, mainly perphenazine, were used only in approximately 21% of the cases. All these atypical

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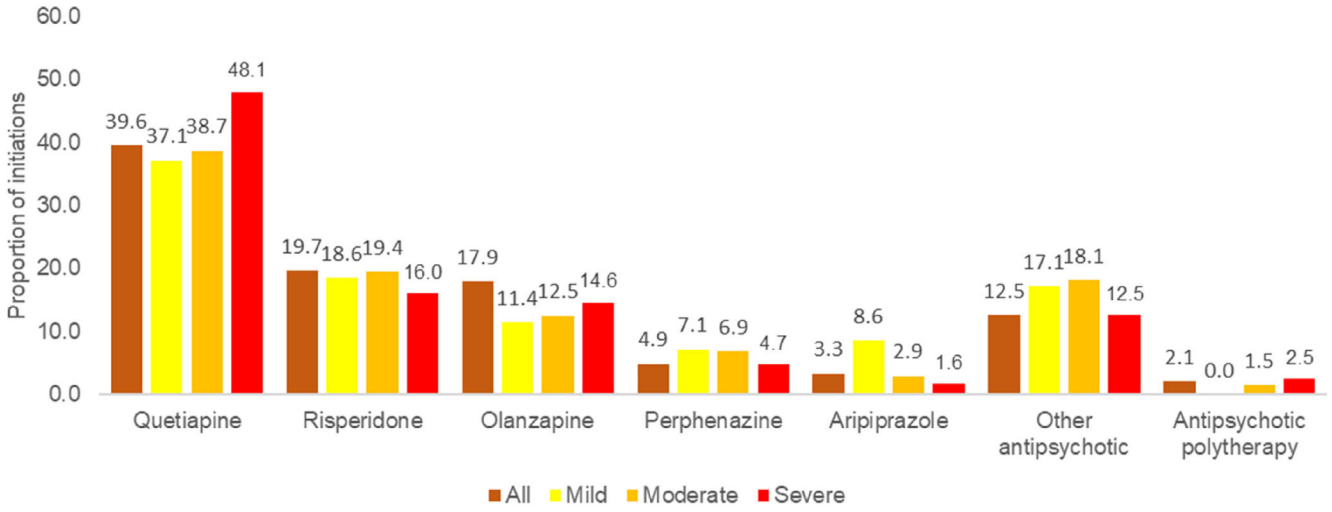

FIGURE 3 Distribution of most common antipsychotic augmentations by severity of depression.

antipsychotics have been found effective as augmentors also in the literature and regarded as first-line augmentation in several guidelines.[33,34]

Quetiapine was the most used AP, and its use was twice as common as the second most common option (risperidone). In the study by Zhou et al.[17] quetiapine was also the most commonly used AP (43.4%), followed by olanzapine (38.8%). Quetiapine has been reported to be effective in depression,[35] and as it is effective also when treating general anxiety disorder,[36] it may provide additional benefit for patients with anxiety. In children and young adults, quetiapine has induced less weight gain and dyslipidemia than olanzapine, but more than aripiprazole, although the authors determined that the strength of evidence is low.[15] In recent meta-analysis of adults with MDD, risperidone and aripiprazole were found more efficacious and accepted than other atypical antipsychotics.[33]

Perphenazine was the only more commonly, although rarely, used first-generation antipsychotic drug in our study. Before the era of atypical antipsychotics, perphenazine and other high-potency typical antipsychotics had been commonly used in combination with antidepressants to treat patients with more severe, agitated or "near psychotic" depressions.[14] However, they have been largely replaced by atypical antipsychotics as these have benefits such as lower rates of extrapyramidal symptoms and risk of tardive dyskinesia compared to first-generation antipsychotics. Its use may be related to old habits by more experienced psychiatrists.

When considering persons with severe depression with psychotic features, some differences emerged compared to other severities of depression. In the psychotic depression group, use of fluoxetine decreased odds of AP augmentation while use of sertraline was associated with AP augmentation. The reason for this is unknown, however we speculate that differences in their receptor binding profiles and half-lives may have an effect. Unlike sertraline, fluoxetine has moderate affinity and an antagonist effect to $5HT_{2c}$ receptors.[37,38] Therefore, fluoxetine may present similar effects as APs. Also, fluoxetine has a markedly longer half-life than sertraline and other SSRIs and sertraline may need higher doses and blood concentrations to have therapeutic effects, thus fluoxetine may retain therapeutic concentrations better than sertraline and other SSRIs, especially in cases of non-optimal adherence.[39] This may lead to better therapeutic efficacy and lower need for augmentation in fluoxetine than sertraline.

4.1 | Strengths and limitations

A nationwide sample of young adults diagnosed with depression is a great strength to this study. Medication use was modeled with PRE2DUP method, which has been shown to provide reliable estimates of drug use.[40] However, we lack data about, for example, possible psychotherapy or family/social support of the cohort. In addition, severity level of depression could not be defined for all persons in the study cohort, leading to relatively large exclusion compared to the whole cohort. With the data sources used we do not know how many patients were prescribed antipsychotics but were not dispensed from pharmacy (primary nonadherence) as the Prescription register data includes only dispensed prescriptions.

5 | CONCLUSION

In conclusion, use of APs as augmentation of antidepressant therapy was common among persons with severe

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depression. Use of TCAs, paroxetine, sertraline or venlafaxine as initial antidepressant were associated with an increased probability of augmentation compared to citalopram. Comorbidities had only small effect to the augmentation. An important finding was that use of bupropion as initial antidepressant was associated with a decreased the risk of augmentation. The reason for this should be more thoroughly addressed in subsequent studies.

Based on these results, use of bupropion (and fluoxetine in case of psychotic depression) as initial AD to treat depression might be advisable in order to decrease the risk of AP augmentation. However, as different ADs have different characteristics in terms of, for example, receptor binding profiles and pharmacokinetics, the choice of initial AD should be individually considered in clinical practice.

CONFLICT OF INTEREST STATEMENT

Pasi Lampela reports no conflicts of interest. Heidi Taipale, Antti Tanskanen, and Jari Tiihonen have participated in research projects funded by grants from Janssen-Cilag and Eli Lilly to their employing institution. Heidi Taipale reports personal fees from Gedeon Richter, Janssen, Lundbeck and Otsuka. Markku Lähteenvuo has received honoraria from Janssen, Janssen-Cilag, Lundbeck, Orion Pharma, Otsuka Pharma, Recordati and Sunovion. Jari Tiihonen has been a consultant and/or advisor to and/or has received honoraria from: Eli Lilly, Evidera, HLS Therapeutics, Janssen-Cilag, Lundbeck, Orion, Otsuka, Mediuutiset, Sidera, Sunovion, and WebMed Global.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13633.

DATA AVAILABILITY STATEMENT

Data collected for this study is proprietary of the Finnish government agencies Social Insurance Institution of Finland and National Institute for Health and Welfare which granted researchers permission and access to data. The data that support findings of this study are available from these authorities, but restrictions apply to the availability of these data. The code used to analyze these data is available upon request by the corresponding author for purposes of reproducing the results.

ETHICS STATEMENT

The research project was approved by pertinent institutional authorities at the Finnish National Institute for Health and Welfare (permission 635/5.05.00/2019), the Social Insurance Institution of Finland (31/522/2019), Finnish Centre for Pensions (19023) and Statistics Finland (TK-53-569-19).

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