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Antidepressant Use and Orthostatic Hypotension in Older Adults Living with Mild-to-Moderate Alzheimer Disease

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Keywords: Antidepressant, Orthostatic Hypotension, Dementia, Alzheimer's Disease, Selective-Serotonin Reuptake Inhibitor, Falls

Key Points:

- Antidepressant medication is frequently listed as causing/exacerbating Orthostatic Hypotension (OH). Older adults with Alzheimer Disease (AD) may be particularly vulnerable to these effects.
- Antidepressant medication use was associated with a significantly greater drop in blood pressure at 5 minutes in older adults with AD
- Selective Serotonin Reuptake Inhibitor (SSRI) use in particular may be a risk factor for classical OH
- Screening older antidepressant users, in particular those with AD, may be important in terms of medication optimisation and falls prevention

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Abstract

Objectives: Antidepressant use is often reported as a risk factor for Orthostatic Hypotension (OH), however this relationship has never been explored in those with mild/moderate Alzheimer Disease (AD), who may represent a particularly vulnerable cohort

Methods: We performed a cross-sectional analysis of baseline data from the NILVAD study. Participants with mild-moderate AD were recruited from 23 centres in 9 countries. Systolic

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and Diastolic Blood Pressure (SBP/DBP) was recorded in the seated position and after both 1 & 5 minutes of standing. OH was defined as a drop of ≥ 20mmHg SBP/≥ 10mmHg DBP. We examined the relationship between antidepressant use, orthostatic BP drop and the presence of OH, controlling for important covariates.

Results: Of 509 participants (72.9 ± 8.3 years, 61.9% female), two-fifths (39.1%; 199/509) were prescribed a regular antidepressant. Antidepressant use was associated with a significantly greater SBP and DBP drop at 5 minutes (β: 1.83, 0.16 – 3.50, p = 0.03 for SBP; β: 1.13, 0.02 – 2.25, p<0.05 for DBP). Selective Serotonin Reuptake Inhibitor (SSRI) use was associated with a significantly greater likelihood of OH (OR 2.0, 1.1-3.6, p = 0.02). Both findings persisted following robust covariate adjustment.

Conclusions: In older adults with AD, antidepressants were associated with a significantly greater SBP/DBP drop at 5 minutes. SSRI use in particular may be a risk factor for OH. This emphasises the need to screen older antidepressant users, and particularly those with AD, for ongoing orthostatic symptoms in order to reduce the risk of falls in this vulnerable cohort.

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Introduction

Whilst antidepressant medication is an efficacious treatment modality in the management of depression in later life[1], a recent Cochrane review has demonstrated limited efficacy for the

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use of antidepressant medication for the treatment of depressive symptoms in those diagnosed with dementia, who may represent a particularly vulnerable cohort[2]. In the largest trial to date examining the use of both sertraline and mirtazapine for depression in AD, there was no significant benefit on depressive symptoms at 13 weeks[3]. Antidepressant medication use in older adults is associated with numerous adverse effects and concerns over safety remain[4]. In fact, the ongoing use of antidepressant medication without appropriate indication is included in criteria for inappropriate medication use in older adults[5].

A frequently cited potential adverse effect of antidepressant medication use is exacerbation of Orthostatic Hypotension (OH)[6]. OH is independently more common in older people and in those with dementia, and is frequently defined by a drop in systolic blood pressure (BP) by 20 mmHg or greater or a drop in diastolic BP by at least 10 mmHg or greater within 3 minutes of standing[7]. As well as producing syncopal symptoms such as dizziness and light-headedness, OH is a significant risk factor for future falls[8]. Further, there is evidence that OH may act as a risk factor for later cognitive decline and dementia in the first instance[9,10].

Whilst the potential risk of antidepressants in causing or exacerbating OH is frequently noted in a clinical context, the number of studies actually investigating this relationship remains low[11]. In a study of over 500 participants over a nine year period, both Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs) were associated with orthostatic hypotension[12]. Further, in a recent study examining the relationship between continuous antidepressant users and a matched control cohort, SSRIs, but not other

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antidepressants were associated with a twofold increased risk of OH[11]. Finally, on detailed analysis of data from the Irish Longitudinal Study on Ageing (TILDA) using beat-to-beat blood pressure measurements, antidepressant use was significantly associated with a large-drop, non-recovery morphology of orthostatic blood pressure behaviour[13].

Whilst the few studies in the literature to date examining the link between antidepressants and OH have focussed on community-dwelling older adults without dementia, those with a diagnosis of dementia may be particularly vulnerable to the adverse orthostatic effects of these medications. OH is more common in older adults with dementia[14] and those with dementia may be particularly vulnerable to the adverse effects of medications[15]. Further, those with dementia have an increased risk of falls[16,17]. However, the orthostatic effects of antidepressants has not been explored in this group, who are frequently prescribed antidepressant medication, despite the evidence reporting limited efficacy in this group.

In the current study, we performed a cross-sectional analysis of baseline data from NILVAD, a randomised controlled trial of the antihypertensive Nilvadipine in mild-to-moderate Alzheimer Disease (AD). We aimed to assess the relationship between antidepressant use and blood pressure behaviour at both 1 and 5 minutes post stand in addition to the presence of OH at 1 minute (classical OH) and 5 minutes (delayed OH)

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Methods

Study Setting

The current study is secondary analysis of baseline data from the NILVAD study. NILVAD was a randomised clinical trial of the antihypertensive *Nilvadipine* in mild/moderate AD. It was an investigator led study which recruited participants from 23 study sites in 9 Countries and received ethical approval from institutional review boards at each country. For details, readers are directed to both the main study protocol[18] and the main results paper[19.]

In short, participants were included if they had a diagnosis of Alzheimer Disease as per the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria. Participants were excluded if they exhibited symptoms suggestive of a current depressive episode. Detailed inclusion and exclusion criteria have been previously published[18]. Of relevance to the current study, participants using β-blockers, α-blockers and calcium-channel blockers were excluded – medications frequently reported to exacerbate orthostatic blood pressure changes and OH[11]. Participants were included if blood pressure measurements were between 100-159 mmHg systolic and 65-99 mmHg diastolic. All participants included in the current analysis met all of the inclusion criteria for the NILVAD trial (the intention-to-treat population of the trial).

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We analysed data from the first two study visits (screening and week 0 visits), prior to randomisation to the study drug/placebo in order to evaluate the association between antidepressant use, orthostatic blood pressure changes and OH, before any potential nilvadipine treatment or trial participation effects may have occurred.

Blood Pressure Measurement & Definition of Orthostatic Hypotension

Participants in the current study had baseline blood pressure assessed at two visits prior to randomisation to the study drug (screening visit and at week 0). At both visits, sitting BP was measured by trained trial staff using a sphygmomanometer after five minutes in the seated position. BP measurement was then repeated after 1 minute and 5 minutes of standing to capture orthostatic BP changes.

In order to analyse baseline BP prior to commencement of the trial, we created a systolic BP (SBP) and diastolic BP (DBP) variable for each participant consisting of the arithmetic mean of both SBP and DBP measurements at screening and week 0 visit. The change in SBP and DBP after 1 minute and 5 minutes standing were obtained by subtracting the seated reading from the reading after 1 minute/5 minutes of standing to obtain a variable SBP/DBP drop. This was calculated for each of the two visits separately. The SBP/DBP drop at both 1 minute/5 minutes from both visits were then averaged to create a mean drop for both

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SBP/DBP for each participant at 1 and 5 minutes and the mean values used in regression analysis (representing the mean drop in SBP/DBP on standing).

In agreement with previous criteria, we defined orthostatic hypotension as a drop in SBP of ≥ 20 mmHg or a drop in DBP of ≥ 10 mmHg on standing[7]. This was computed for each visit (screening and week 0) separately at both 1 minute (defined as classical OH: cOH) and 5 minutes (defined as delayed OH: dOH). Participants were considered to have cOH or dOH if they met the above criteria for OH on at least one of the two baseline visits.

Antidepressant and Other Medication Use

A comprehensive list of current medication was obtained from participants at baseline. Anatomic Therapeutic Classification (ATC) codes were applied to participant medication lists in duplicate by two physicians. Antidepressants were coded for by the stem N06 with classes coded as follows: N06AA for Tricyclic Antidepressants (TCAs), N06AB for Selective-Serotonin Reuptake Inhibitors (SSRIs), N06AX16/N06AX21 for Serotonin-Noradrenaline Reuptake Inhibitors (SNRI) and the remainder of the N06AX codes as "other antidepressants", including Mirtazepine (N06AX11) and Trazodone (N06AX05).

We created a list of established "culprit" medications which have known influence on orthostatic blood pressure changes. Briefly, these included cardiovascular drugs (C02, C03, C07, C08, C09), antipsychotic medication (N05A) and other drugs known to exacerbate OH

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(such as tamsulosin, oxybutynin and tizanidine), in accordance with previous literature[6,11]. In order to account for total medication burden, the total number of prescribed medications was calculated individually for each participant.

Covariates

Routine demographic information was obtained in a standard fashion at study enrolment (age, sex, Body Mass Index (BMI), years of education, years since AD diagnosis). A comprehensive medical history was also obtained from participants at baseline. The total number of medical comorbidities was calculated per participant to allow us to control for total comorbidity in regression models. Further, participants' medical histories were manually screened in duplicate and history of diagnosed depression/anxiety recorded, the most common reasons for antidepressant use, in order to allow us control for confounding by indication. Dementia severity was assessed using the Clinical Dementia Rating – Sum of Boxes (CDR-Sb) and cognitive severity measured using the Alzheimer's Disease Assessment Scale – Cognitive Subsection (ADAS-Cog) in a standardised fashion.

Statistics

Descriptive statistics were reported as means (± standard deviation) or medians (interquartile range) where appropriate. Proportions were expressed as percentages. Univariate statistics

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employed t-tests and ANOVA (or Kruskall-Wallis H test for non-parametric data) tests. Proportions were analysed using the chi-square test.

We used mixed effects linear models in order to assess effect of medication usage on the dependent variable, mean drop in systolic or diastolic blood pressure at 1 minute (averaged over the two initial visits), with study site as a random effect. In the first instance, associations were tested unadjusted (model 1), followed by adjustment for age, sex, BMI, baseline seated blood pressure (SBP/DBP as appropriate) and a past medical history of depression/anxiety (model 2). In a final model, we incorporated use of other medications with potential effects on blood pressure ("culprit" medications as a above) in addition to total number of medical comorbidities and total number of medications. In order to analyse the effect of antidepressant use on the prevalence of orthostatic hypotension, we performed mixed effects logistic regression, again with study site as a random effect. We incorporated the same covariates as above in models 1-3.

In the first instance, we tested the association of antidepressant as a binary variable with the outcome of interest. Consistent with previous reports showing class-specific effects of antidepressant medication on orthostatic BP changes[11], we performed analysis for the most common three sub-classes: SSRIs, mirtazapine and SNRIs in order to capture any class specific effects not seen in the overall analysis. Statistical significance in all instances was considered $p<0.05$.

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Results

Participant Characteristics

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Overall, 509 participants had baseline assessment completed. In the cohort overall, the mean age was 72.9 (±8.3) and the majority of participants were female (61.9%; 315/509). Median years since AD diagnosis was 1.1 years (0.5-2.3). Baseline AD severity was 5.3 (±2.8) measured using the CDR-Sb. Baseline cognitive impairment measured using the ADAS-Cog was 34.5 (±10.6).

Antidepressant Medication Use

Overall, two-fifths (39.1%; 199/509) were prescribed a regular antidepressant medication. A small minority were prescribed more than one antidepressant (16/509, 3.1%), with no participant prescribed more than one agent from the same class. Prescription of antidepressant medication significantly differed by country, with use highest in France (62.1% 36/58), Italy (60.0%; 33/55), Greece (43%, 43/100) in comparison to the UK (20%, 13/65) and the Netherlands (23.1%, 18/78) ($\chi^2 = 47.9$, $p<0.001$).

The most common antidepressant class, prescribed in nearly three-quarters of participants was SSRIs (147/199; 73.9%), followed by mirtazapine (N = 24/199; 12.1%), SNRIs (22/199; 11.1%), Trazadone (16/199; 8.0%) and TCAs (7/199; 3.5%). Within the largest class (SSRIs) the most common medications prescribed were escitalopram (N = 49) and citalopram (N = 45) followed by sertraline (N = 34). Baseline characteristics by antidepressant medication prescription, and appropriate univariate statistics are provided in **Table 1.**

Antidepressant Use and Orthostatic Blood Pressure Drop

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Overall there was no significant difference in seated systolic (SBP) or diastolic (DBP) blood pressure in those prescribed an antidepressant vs those not prescribed an antidepressant [138.0 (± 12.6)/77.1 (± 7.6) mmHg for non-users vs 136.9 (± 11.9)/76.9 (±7.6) mmHg for antidepressant users] (t = 1.5, p = 0.1 for SBP, t = 0.3, p = 0.4 for DBP).

Overall, antidepressant use was not associated with a greater drop in SBP or DBP at 1 minute under the unadjusted model or either adjusted models. Analysis repeated by antidepressant subclass also revealed no significant results and effect estimates are included alongside those for antidepressant use in **Table 2.** On analysing SBP/DBP drop at 5 minutes, there was no association between antidepressant use and either drop in SBP or DBP. Under model 2, antidepressant use was associated with a greater BP drop at 5 minutes (+1.7 mmHg [0.1 - 3.4], p = 0.04 greater drop for SBP; +1.13 mmHg [0.1 - 2.2], p = 0.04 for DBP). Finally, under model 3, antidepressant use was also associated with a significantly greater BP drop at 5 minutes (+1.8 mmHg [0.2 - 3.5], p = 0.03 greater drop for SBP; +1.13 mmHg [0.2 - 2.3], p = 0.04 for DBP). For results, **see Table 3.**

Antidepressant Use and Orthostatic Hypotension

Overall, 15.4% (N = 78/509) of study participants met criteria for cOH measured at 1 minute at either visit. The prevalence of OH was higher in those prescribed an antidepressant (17.6%, 35/164) than those without antidepressant use (13.9%, 43/266). The prevalence of

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OH was highest in those using SSRIs (20.6%, 28/136) ($\chi^{2 =}$ 4.1, p = 0.04) followed by mirtazapine (14.3%, 3/21) (χ^2 = 0.16, p = 0.69) and SNRIs (10.5%, 2/19) (χ^2 = 0.7, p = 0.41).

There was no association between antidepressant use and cOH under an unadjusted model (OR 1.3, 0.8 – 2.2, p = 0.3; model 1) or under either model 2 (OR 1.5, 0.9 – 2.7, p = 0.1) or 3 (OR 1.5, 0.8 – 2.7, p = 0.2). However, on analysis of antidepressant classes, SSRIs, but not other antidepressants were significantly associated with the presence of cOH under the unadjusted model (OR 1.7, 1.0 – 2.8, p = 0.04; model 1) and under both adjusted models (OR 2.0, 1.1 – 3.7, p = 0.01 for model 2, OR 2.0, 1.1 – 3.6, p = 0.02 for model 3). See **Table 4**

Finally, the relationship between antidepressant use and dOH was explored. In the overall cohort, 15.2% (77/509) had dOH at either screening/baseline visit. The prevalence of dOH was similar in those taking antidepressants (14.6%, N = 26/199) and antidepressant non-users (15.5%, N = 48/309) (χ^2 = 0.09, p = 0.8). Under model 1 there was no association between antidepressant use and dOH (OR 0.9, 0.5 -1.5, p = 0.7). Similarly, no association was seen under either adjusted model (OR = 1.5, 0.9 – 2.7, p = 0.9 for model 2; OR 0.9, 0.5 – 1.8, p = 0.9 for model 3).

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Discussion

In the current study, we analysed the relationship between antidepressant use and orthostatic BP behaviour over two visits. This is the first study to assess this relationship in those with dementia, a group who may be particularly vulnerable to polypharmacy and the adverse effects of antidepressant medication. Consistent with previous reports in the literature[11,13], we demonstrated a significant association between SSRI use and cOH and a significant association between antidepressant use and an effect of antidepressant use on delayed BP recovery on standing (at 5 minutes).

There was a significant association between antidepressant use and both SBP and DBP at 5 minutes after standing. These findings support previous reports which demonstrated an association between antidepressant use and a large-drop, non-recovery pattern of orthostatic BP behaviour in community-dwelling older adults[13]. Our findings echo this BP behaviour and add further insight to the orthostatic effect of ongoing antidepressant use in older adults. It is also worthy of note that this drop in BP did not necessarily translate into an increased risk of delayed OH in the current analysis. This may be due to the strict cut-off we used for defining

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orthostatic hypotension in the current analysis. It also may be a result of our sphygmomanometer-based oscilometric measurement and not phasic beat-to-beat finometer-based BP measurement. Nevertheless, our findings demonstrate a significant effect BP drop at 5 minutes in antidepressant users.

We also observed a significant association between SSRI use and the prevalence of cOH, measured at 1 minute. This finding is consistent those of Briggs et al. who demonstrated an SSRI-specific association with cOH in a large community study[11]. We also observed no association between SNRIs, mirtazapine and other antidepressants on orthostatic blood pressure behaviour and the prevalence of cOH, however, our study may have been underpowered to detect such changes in these subgroups. While statistically non-significant, there was a greater overall drop in systolic and diastolic BP at 1 minute post standing, adding further evidence to the link between antidepressant use and orthostatic BP behaviour in some individuals.

The association between SSRI use and OH is noteworthy and is consistent with previous research. SSRIs are frequently viewed as the safest choice of antidepressant class for use in older patients, however use has been associated with syncope, fractures and unexplained falls [20-22]. Use of SNRIs on the other hand has not been reported to increase risk of OH, although having a low number of participants on these medications in the current study may mean that we were underpowered to detect these changes[23-24.] . All major classes of antidepressants have been reported to cause or exacerbate OH, and based on the current study, there is

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insufficient evidence to conclude that any individual class poses more or less risk than the others. Further, an important unanswered question concerns the mechanism by which antidepressants may cause OH, which could include effects of psychomotor function and gait speed, effects on neurotransmission and vascular tone and also via other effects such as hyponatraemia. This is an area where further research is warranted.

The prevalence of antidepressant use in the current study is particularly striking, as is the difference between prescribing rates in the different Countries. The reasons for these differences are beyond the scope of the current study but may reflect different international practice between individual study sites.

Our study has several notable strengths including its international nature (conducted at 23 sites across 9 countries) in addition to the wealth of information captured on individual participants. It also adds a unique perspective in that participants using many medications known to exacerbate OH were excluded, as were participants with a history of significant cardiovascular disease, enabling us to examine the influence of antidepressants on orthostatic BP free from these confounding influences. We also recorded blood pressure across 2 separate visits and analysed BP behaviour as the mean of readings across these two visits, enabling a more accurate picture of overall BP behaviour. Finally, we were able to test this association at baseline, before randomisation to the study drug, in order to exclude any treatment or trial participation effects.

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However, our study has several limitations. In the first instance, we recorded blood pressure using a manual sphygmomanometer which is reflective of how OH is measured in the majority of clinical settings. Continuous phasic beat-to-beat monitoring of blood pressure over time using a finometer identifies more rapid changes in BP with each cardiac cycle, allowing continuous data of BP behaviour whilst moving from seated to a standing position. However, we did analyse BP behaviour over two separate baseline visits in order to enable a more accurate estimate of BP prior to randomisation to the study drug. Further our study is limited by its cross-sectional nature. Further longitudinal studies in this at risk group are warranted. We are also limited by several confounding factors such as polypharmacy, frailty and comorbidity in this group, however, we attempted to control for this confounding in the current analysis. We controlled for total medication burden, culprit medication use and total number of medical comorbidities, attempting to capture the contribution of these important confounders.

In conclusion, we performed the first analysis of the association between antidepressant use and OH in those with mild-to-moderate AD. We demonstrated a significant association between antidepressant use and orthostatic blood pressure drop at 5 minutes post-stand in addition to a significant association between SSRI use and classical orthostatic hypotension. Our results have important implications for optimal prescribing to treat depression in people with dementia, living with dementia, and that consideration in choosing the most appropriate antidepressant therapy should include factoring in concurrent symptoms of recurrent falls, syncope, and orthostatic hypotension.

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Conflicts of Interest

The authors have no conflict of interest to report

Data Availability

Because of agreements within the Nilvad consortium, the data that support the findings of this cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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Tables

	No Antidepressant (N = 310)	SSRI (N = 147)	Mirtazepine (N = 24)	SNRI (N = 22)	Other Antidepressant (N = 23)	Significance
Age, Yrs (SD)	73.5 (8.2)	71.5 (8.7)	72.2 (5.2)	72.2 (4.9)	74.4 (8.1)	F = 1.55, p = 0.18
Sex, Female (%)	180 (57.1%)	89 (28.3%)	14 (4.4%)	15 (4.8%)	17 (5.4%)	χ^2 = 6.61, p = 0.16
BMI, kg/m^2 (SD)	25.0 (4.3)	26.6 (4.4)	24.2 (2.7)	25.7 (3.4)	25.1 (4.3)	F = 3.97, p = 0.03*
Education, Yrs (SD)	16.9 (4.2)	15.8 (4.1)	17.6 (4.1)	15.3 (4.7)	14.4 (3.2)	F = 3.67, p<0.001**
Diagnosis Duration, Yrs (SD)	1.6 (1.7)	1.6 (1.7)	1.5 (1.6)	2.1 (1.8)	2.00 (1.8)	F = 0.56, p = 0.69
Total Medications, Median (IQR)	5 (3-6)	6 (4-7.5)	6 (4-8)	5 (4-8)	6 (5-8)	χ^2 = 25.37, p <0.001**
Total Comorbidities, Median (IQR)	3 (2-5)	4 (3-6)	3 (2-5)	4 (3-5)	4 (3-6)	χ^2 = 16.03, p = 0.003**
Baseline ADAS-Cog (SD)	33.4 (10.0)	36.2 (11.3)	31.38 (9.7)	39.9 (10.1)	38.4 (12.5)	F = 3.92, p = 0.01*
Baseline CDR-Sb	5.0 (2.7)	5.6 (2.8)	4.8 (2.0)	6.8 (3.1)	6.2 (3.2)	F = 2.41, p = 0.05

Table 1. Baseline Demographic and Clinical Characteristics of Participants by Antidepressant Class Use. ANOVA, Kruscal-Wallis tests and Chi-square tests were used to compare differences between users of the different subclasses in comparison to those not using any antidepressants. * = p<0.05, ** = p <0.001. SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Selective Serotonin-Noradrenaline Reuptake Inhibitor; SD: Standard Deviation; IQR: Interquartile range; BMI: Body Mass Index; ADAS-Cog: Alzheimer Disease Assessment Scale – Cognitive Subsection; CDR-Sb: Clinical Dementia Rating – Sum of Boxes

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Blood Pressure Drop at 1 Min						
Systolic Blood Pressure	**Model 1 - SBP**		**Model 2 - SBP**		**Model 3 - SBP**	
	β Coef (95% CI)	**P**	**β Coef (95% CI)**	**P**	**β Coef (95% CI)**	**P**
Antidepressant Use	0.93 (-0.50 – 2.37)	0.20	1.31 (-0.11 – 2.72)	0.07	1.25 (-0.19 – 2.70)	0.09
SSRI	0.72 (-0.83 – 2.26)	0.37	0.93 (-0.72 – 2.59)	0.27	0.63 (-1.03 – 2.29)	0.46
Mirtazepine	0.27 (-2.95 – 3.48)	0.87	0.29 (-2.86 – 3.45)	0.86	0.14 (-2.97 – 3.25)	0.93
SNRI	1.95 (-1.41 – 5.32)	0.26	2.78 (-0.65 – 6.21)	0.11	2.98 (-0.38 – 6.35)	0.08
Age			-0.00 (-0.09 – 0.08)	0.92	0.02 (-0.07 – 0.11)	0.67
Gender			-0.09 (-1.45 – 1.28)	0.90	-0.08 (-1.44 – 1.27)	0.91
BMI			-0.32 (-0.48 - -0.16)	0.01*	-0.28 (-0.44 – 0.12)	0.01*
Baseline BP			0.11 (0.06 – 0.17)	0.01*	0.13 (0.07 – 0.18)	0.01*
History of Depression/Anxiety			-0.16 (-2.04 – 1.71)	0.86	-0.16 (-2.04 – 1.71)	0.86
Culprit Medications					2.73 (1.16 – 4.26)	0.01*
Total Comorbidities					-0.27 (-0.60 – 0.07)	0.12
Total Medications					0.06 (-0.22 – 0.38)	0.67
Diastolic Blood Pressure	**Model 1 - DBP**		**Model 2 - DBP**		**Model 3 - DBP**	
	β Coef (95% CI)	**P**	**β Coef (95% CI)**	**P**	**β Coef (95% CI)**	**P**
Antidepressant Use	0.57 (-0.46 – 1.61)	0.28	1.04 (-0.10 – 2.19)	0.08	1.08 (-0.09 – 2.26)	0.07
SSRI	0.55 (-0.57 – 1.67)	0.34	1.03 (-0.19 – 2.24)	0.09	1.04 (-0.20 – 2.29)	0.10
Mirtazepine	-0.79 (-3.11 – 1.53)	0.51	0.48 (-2.82 – 1.87)	0.69	-0.45 (-2.86 – 1.90)	0.71
SNRI	-0.11 (-2.54 – 2.33)	0.93	0.27 (-2.29 – 2.82)	0.83	0.33 (-2.22 – 2.88)	0.80

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Age			0.07 (0.00 – 0.13)	0.03*	0.08 (-0.01 – 0.15)	0.02*
Gender			0.66 (-0.39 – 1.70)	0.22	0.66 (-0.39 – 1.71)	0.22
BMI			-0.09 (-0.21 – 0.34)	0.16	-0.08 (-0.20 – 0.05)	0.22
Baseline BP			0.23 (0.16 – 0.30)	0.01*	0.23 (-0.16 – 0.31)	0.01*
History of Depression/Anxiety			-0.78 (-2.27 – 0.53)	0.224	-0.83 (-2.23 – 0.60)	0.25
Culprit Medications					-0.30 (-1.44 – 0.86)	0.62
Total Comorbidities					0.01 (0.25 – 0.25)	0.99
Total Medications					-0.08 (-0.29 – 0.13)	0.45

Table 2. Mean Drop in Orthostatic Blood Pressure at 1 Minute Blood Pressure and Antidepressant Use. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, BP: Blood Pressure, SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Noradrenaline Reuptake Inhibtor. * = $p<0.05$

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Blood Pressure Drop at 5 Min						
Systolic Blood Pressure	**Model 1 - SBP**		**Model 2 - SBP**		**Model 3 - SBP**	
	β Coef (95% CI)	**P**	**β Coef (95% CI)**	**P**	**β Coef (95% CI)**	**P**
Antidepressant Use	0.99 (0.48 – 2.46)	0.19	1.73 (0.08 – 3.39)	0.04*	1.83 (0.16 – 3.50)	0.03*
SSRI	0.62 (-0.97 – 2.21)	0.45	0.93 (-0.72 – 2.59)	0.42	1.40 (-0.40 – 3.16)	0.12
Mirtazepine	-1.29 (-4.52 – 2.06)	0.45	0.29 (-2.86 – 3.45)	0.89	-1.45 (-4.86 – 1.95)	0.40
SNRI	2.66 (-0.83 – 6.13)	0.14	2.78 (-0.65 – 6.21)	0.01*	3.75 (-0.11 – 7.40)	0.04
Age			0.04 (-0.13 – 0.05)	0.42	0.01 (-0.09 – 0.10)	0.96
Gender			0.01 (-1.63 – 1.42)	0.89	-0.05 (-1.55 – 1.47)	0.96
BMI			-0.28 (-0.45 - -0.11)	0.01*	-0.23 (-0.40 – 0.54)	0.01*
Baseline BP			0.14 (0.08 – 0.20)	0.01*	0.15 (0.09 – 0.21)	0.01*
History of Depression/Anxiety			-0.34 (-2.33 – 1.66)	0.74	-0.06 (-2.03 – 1.91)	0.95
Culprit Medications					1.85 (0.21 – 3.51)	0.03*

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Total Comorbidities					-0.30 (-0.65 – 0.06)	0.10
Total Medications					-0.03 (-0.33 – 0.27)	0.86
Diastolic Blood Pressure	**Model 1 - DBP**		**Model 2 - DBP**		**Model 3 - DBP**	
	β Coef (95% CI)	**P**	**β Coef (95% CI)**	**P**	**β Coef (95% CI)**	**P**
Antidepressant Use	0.75 (-0.24 – 1.73)	0.14	1.13 (0.05 – 2.22)	0.04*	1.13 (0.02 – 2.25)	0.05*
SSRI	0.57 (-0.49 – 1.63)	0.29	0.99 (-0.15 – 2.15)	0.09	1.04 (-0.20 – 2.29)	0.10
Mirtazepine	-0.78 (-3.00 – 1.43)	0.49	-0.36 (-2.59 – 1.88)	0.76	-0.45 (-2.86 – 1.90)	0.71
SNRI	0.72 (-1.59 – 3.02)	0.54	-0.61 (-1.81 – 3.04)	0.62	0.33 (-2.22 – 2.88)	0.80
Age			0.01 (-0.06 – 0.07)	0.81	0.01 (-0.06 – 0.07)	0.80
Gender			0.93 (-0.06 – 1.93)	0.07	0.93 (-0.06 – 1.92)	0.07
BMI			0.03 (-0.08 – 0.15)	0.57	0.04 (-0.08 – 0.15)	0.54
Baseline BP			0.22 (0.015 – 0.02)	0.01*	0.22 (0.15 – 0.29)	0.01*
History of Depression/Anxiety			-1.05 (-2.41 – 0.30)	0.13	-1.06 (-2.42 – 0.29)	0.12
Culprit Medications					-0.16 (-1.26 – 0.94)	0.77
Total Comorbidities					0.06 (-0.18 – 0.30)	0.63
Total Medications					-0.05 (-0.25 – 0.15)	0.62

Table 3. Mean Drop in Orthostatic Blood Pressure at 5 Minutes Blood Pressure and Antidepressant Use. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, BP: Blood Pressure, SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Noradrenaline Reuptake Inhibtor. * = $p<0.05$

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Classical OH (cOH): [1 Minute]						
	Model 1		**Model 2**		**Model 3**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Antidepressant Use	1.32 (0.81 – 2.15)	0.27	1.54 (0.87 – 2.73)	0.13	1.49 (0.82 – 2.69)	0.19
SSRI	1.68 (1.01 – 2.78)	0.04*	2.03 (1.13 – 3.65)	0.01*	1.98 (1.08 – 3.61)	0.02*

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Mirtazepine	0.79 (0.23 – 2.74)	0.71	0.93 (0.27 – 3.25)	0.91	0.93 (0.26 – 3.28)	0.90
SNRI	0.53 (0.12 – 2.32)	0.40	0.70 (0.16 – 3.14)	0.64	0.70 (0.15 – 3.19)	0.65
Age			1.01 (0.98 – 1.04)	0.62	1.01 (0.97 – 1.04)	0.71
Gender			0.95 (0.55 – 1.64)	0.86	0.93 (0.54 – 1.61)	0.80
BMI			0.98 (0.92 – 1.05)	0.56	0.98 (0.92 – 1.05)	0.56
History of Depression/Anxiety			0.75 (0.36 – 1.57)	0.44	0.74 (0.35 – 1.55)	0.42
Culprit Medications					0.88 (0.49 – 1.60)	0.68
Total Comorbidities					1.06 (0.94 – 1.20)	0.32
Total Medications					0.98 (0.88 – 1.10)	0.75
Delayed OH (dOH) [5 minutes]						
	Model 1		**Model 2**		**Model 3**	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
Antidepressant Use	0.91 (0.53 – 1.53)	0.72	1.54 (0.87 – 2.73)	0.93	0.95 (0.51 – 1.79)	0.87
SSRI	0.81 (0.46 – 1.46)	0.50	0.82 (0.42 – 1.61)	0.57	0.80 (0.40 – 1.58)	0.51
Mirtazepine	1.06 (0.85 – 1.34)	0.71	1.10 (0.99 – 1.07)	0.49	1.09 (0.98 – 1.06)	0.50
SNRI	1.84 (0.62 – 5.42)	0.27	1.76 (0.52 – 5.94)	0.36	0.70 (0.15 – 3.19)	0.65
Age			1.03 (0.90 – 1.07)	0.10	1.02 (0.99 – 1.06)	0.20
Gender			0.74 (0.42 – 1.31)	0.30	0.72 (0.41 – 1.28)	0.27
BMI			0.99 (0.92 – 1.06)	0.73	0.98 (0.92 – 1.05)	0.63
History of Depression/Anxiety			0.99 (0.45 – 2.16)	0.98	0.95 (0.43 – 2.06)	0.89
Culprit Medications					0.95 (0.51 – 1.76)	0.86
Total Comorbidities					1.11 (0.97 – 1.26)	0.12
Total Medications					0.98 (0.87 – 1.10)	0.72

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Table 4. Logistic Regression Examining the Impact of Antidepressant Use and classical OH/delayed OH. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, BP: Blood Pressure, SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin-Noradrenaline Reuptake Inhibitor. * = $p<0.05$

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