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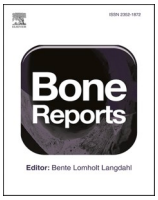

Antipsychotic medication use in association with quantitative heel ultrasound (QUS)

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ABSTRACT

Purpose: Antipsychotic medication use has been associated with decreased bone mineral density; however, less is known whether antipsychotics affect other parameters of bone health. Therefore, the aim of this study was to investigate the association between antipsychotic medication use and quantitative heel ultrasound (QUS) in a population based sample of men and women.

Methods: Thirty-one antipsychotic users and 155 non-users matched for age and sex were drawn from the Geelong Osteoporosis Study. QUS was undertaken and included the parameters: Broadband ultrasound attenuation (BUA), speed of sound (SOS) and stiffness index (SI). Current medication use, lifestyle factors, anthropometry and socio-economic status were collected. Generalized Estimation Equation models were conducted to determine associations between antipsychotic medication use and each of the QUS parameters, adjusting for covariates.

Results: Antipsychotic users were less active, consumed less alcohol, were more likely to smoke and take antidepressants; otherwise, the groups were similar. After adjusting for age, sex and weight, antipsychotic users had a 7.7 % lower mean BUA [108.70 (95 % CI 104.26–113.14) vs. 116.42 (95 % CI 115.48–117.37) dB/MHz, $p = 0.005$] and 7.4 % lower mean SI [89.92 (95 % CI 86.89–92.95) vs. 97.30 (95 % CI 96.48–98.12) %, $p < 0.001$] compared to non-users. Differences in mean SOS between antipsychotic users and non-users failed to reach statistical significance ($p = 0.07$).

Conclusion: Antipsychotic use was associated with lower QUS parameters. The risk of bone deterioration should be considered when antipsychotics are prescribed.

1. Introduction

The 2020–2021 National Study of Mental Health and Wellbeing reported that approximately 43.7 % of Australians have a mental or behavioral condition (National Study of Mental Health and Wellbeing, 2022), with 4.5 million (17.7 %) having received a prescription for an agent used to treat (Australian Institute of Health and Welfare, 2022). Between 2011 and 2018, the number of Australians prescribed a psychotropic medication increased from 25.6 to 36.2 in every 1,000 persons (Klau et al., 2022); including antipsychotics, predominantly used for treating psychosis. The number of Australians prescribed one or more antipsychotics increased from about 261,000 in 2005 to 422,000 in 2021 (Australian Institute of Health and Welfare, 2022). Common side effects of antipsychotic use include weight gain, diabetes, cognitive impairment, falls and sedation (Stroup and Gray, 2018). More recently, antipsychotic use has been associated with reduced bone mineral density (BMD) and an increased risk of osteoporosis and subsequent fracture (Graham et al., 2011; Azimi Manavi et al., 2023).

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Osteoporosis is a systemic skeletal disease characterized by low bone mass and architectural deterioration of bone, which is associated with an increased vulnerability to fracture (Hendrickx et al., 2015). Dual-energy x-ray absorptiometry (DXA) is the most widely used tool to determine BMD and diagnose fracture risk; however, it has limitations including a lack of information on bone structure and strength, accessibility, cost and radiation exposure (Glüer, 1997). Other methods have emerged that address many of the aforementioned limitations.

Quantitative heel ultrasound (QUS) is an alternative to DXA that utilizes sound waves beyond the audible threshold (>20 kHz) to characterize bone tissue (Chin and Ima-Nirwana, 2013). Additional information on bone structure is attained across three parameters; broadband ultrasound attenuation [BUA (dB/MHz)], reflecting microarchitecture and bone density; speed of sound [SOS (m/s)], reflecting elasticity and bone density; and stiffness index [SI (%)] a calculated parameter combining SOS and BUA (Chin and Ima-Nirwana, 2013). A meta-analysis including 21 prospective studies found QUS to be a good predictor of fracture risk in men and women (Moayyeri et al., 2012). QUS has also been shown to predict fracture independent of other measures of bone health (Fracture Risk Assessment Tool, BMD, and trabecular bone score), with authors concluding QUS is a useful screening tool in osteoporosis management (Métrailler, 2023).

Given the growing population prescribed antipsychotics for both on- and off-label indications, the associated burden and consequence of osteoporosis, and the dearth of literature investigating the impact of these agents on other parameters of bone health, this study aimed to investigate the association between antipsychotic use and QUS in men and women residing in south-eastern Australia.

2. Materials and methods

2.1. Participants

This cross-sectional study was conducted using data from adults participating in the Geelong Osteoporosis Study (GOS), an ongoing population-based study in south-eastern Australia. Initially, 1,494 women (response 77.1 %) and 1,540 men (response 67 %) were randomly-selected from electoral rolls and invited to participate between 1994 and 1997 and 2001 and 2006, respectively (Pasco et al., 2012). A further 246 women aged 20–29 years were recruited in 2005 to supplement the full adult age range (Pasco et al., 2012). Most participants (98 %) were Caucasian. Additional methodological details of the cohort are published elsewhere (Pasco et al., 2012).

Participants who had undergone a heel QUS and reported concurrent antipsychotic use were identified as antipsychotic users (n = 31). Age- and sex-matched, non-users were randomly selected on a 1–5 basis (n = 155) from participants who had not used antipsychotics. Participants provided written informed consent.

2.2. Data

For all participants, both outcome and exposure variables were collected at the same assessment.

2.3. Outcome variable

Each participant underwent a QUS (Achilles Insight Ultra-sonometer, SL164E 5_04, GE Lunar, Madison, WI, USA) of the left heel. QUS parameters, BUA and SOS were measured, with SI automatically calculated by the software. Trained technicians carried out all examinations and performed daily calibrations of the machine.

2.4. Exposure variables

Current medication use and duration were documented. For accuracy, participants were asked to bring their medications or scripts to the appointment. Antipsychotics and medications known to affect bone were required for analyses. The medications known to affect bone were grouped into those with a positive (antiresorptive agents, hormone replacement therapy and calcium or vitamin D supplements) or negative impact (oral glucocorticoids, thyroid hormones and antidepressant agents) to test in multivariable models.

Alcohol consumption (g/day) was determined using a validated food frequency questionnaire (Giles and Ireland, 1996). Physical activity was documented on a 7-point scale based on Metabolic Equivalent of Task Values (Ainsworth et al., 1993) and categorized as 'active' if participants completed regular vigorous to light exercise or 'inactive' if no appreciable exercise was undertaken. Current cigarette smoking was self-reported. Height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively.

Socio-economic status (SES) was defined using Socio-Economic Index for Areas (SEIFA) index scores from the 2006 Australian Bureau of Statistics census data. SEIFA scores were applied in determining an Index of Relative Socio-economic Advantage and Disadvantage (IRSAD), accounting for low to high income level and type of occupation. Resulting scores ranged from 1 to 5, with 1 representing most disadvantaged and 5 most advantaged (Brennan et al., 2010).

2.5. Statistical analysis

Differences in participants characteristics were identified using *t*-tests and Kruskal-Wallis for parametric and non-parametric continuous variables, respectively. Discrete variables were analysed using chi-square tests or Fisher's exact tests if expected cell counts were less than five.

The association between antipsychotic use (exposure) and each of the QUS parameters (outcomes) were examined using Generalized Estimating Equations (GEE) models, with marginal model-adjusted mean difference and 95 % confidence intervals (CI) presented. The GEE models accounted for the matching structure (i.e., age and sex) using an exchangeable covariate pattern. Age categories (20–39, 40–49, 50–59, 60–69, ≥70 years) and sex were included as factors in the models. Each QUS parameter (BUA, SOS and SI) was modelled separately and potential confounders including weight, height, alcohol consumption, activity level, smoking, SES, duration of antipsychotic use and medications known to affect bone were tested using a backwards stepwise approach and only significant variables were retained in the model ($p < 0.05$). All two-way interactions were tested.

Partial eta squared (ηp^2) effect sizes for general linear models were calculated to determine the strength of associations. Cut offs were set as small (≥0.01), medium (≥0.06) and large (≥0.14) (Draper, n.d.).

SPSS (version IBM 28; SPSS, Armonk, NY: IBM Corp) and Minitab (version 18; Minitab, State College, Pennsylvania) were used for analyses.

3. Results

There were 31 antipsychotic users (51.6 % men) and 155 non users (51.6 % men). Antipsychotic users were more likely to smoke, use antidepressants, be less active and consume less alcohol than non-users; the groups were similar in regards to height, weight, SES, use of medications known to positively impact bone and unadjusted QUS values (Table 1).

Antipsychotics used included Olanzapine (n = 11, 35.48 %), Quetiapine (n = 11, 35.48 %), Paliperidone (n = 2, 6.45 %), Aripiprazole (n = 2, 6.45 %), Trifluoperazine (n = 2, 6.45 %), Clozapine (n = 1, 3.23 %), Haloperidol (n = 1, 3.23 %) and Risperidone (n = 1, 3.23 %). Median duration of antipsychotic use was 36 months (IQR 11.5–72.5).

Following adjustment for age, sex and weight, antipsychotic users had a 7.7 % lower mean BUA and 7.4 % lower mean SI compared to non-users. Activity level, alcohol consumption, height, smoking, SES, duration of antipsychotic use and medications known to positively and

Table 1
Characteristics of antipsychotic users and non-users. Values are given as median (interquartile range), mean (standard deviation) or n (%).

	Antipsychotic users	Non-users	p
	n = 31	n = 155	
Age (years)	51.3 (35.9–63.4)	50.3 (37.0–60.9)	0.948
Male	16 (51.6 %)	80 (51.6 %)	1
Weight (kg)	84.1 (68.0–98.2)	80.0 (67.8–91.0)	0.239
Height (cm)	170.1 ± 8.6	170.0 ± 9.4	0.554
Smoking (current)	10 (32.2 %)	17 (11.2 %)	0.003
Mobility (active)	17 (54.8 %)	124 (81.0 %)	0.002
Alcohol intake (g/day)	1.0 (0.0–13.7)	6.7 (1.2–20.2)	0.015
Socioeconomic status			0.692
Quintile 1 (lowest)	6 (19.3 %)	25 (16.2 %)	
Quintile 2	8 (25.8 %)	30 (19.5 %)	
Quintile 3	6 (19.3 %)	44 (28.6 %)	
Quintile 4	7 (22.6 %)	27 (17.5 %)	
Quintile 5	4 (12.9 %)	28 (18.2 %)	
Medication use (current)			
Bone positive medications			
Antiresorptive agent	0 (0.0 %)	3 (1.9 %)	1
Hormone therapy	1 (3.2 %)	3 (1.9 %)	0.520
Calcium/vitamin D supplement	8 (25.8 %)	26 (16.8 %)	0.235
Bone negative medications			
Oral glucocorticoids	0 (0.0 %)	3 (1.9 %)	1
Thyroid hormones	0 (0.0 %)	11 (7.1 %)	0.126
Antidepressants	14 (45.1 %)	19 (12.2 %)	<0.001
Unadjusted QUS values			
BUA (dB/MHz)	110.8 ± 23.1	116.9 ± 15.4	0.163
SOS (m/s)	1566.5 ± 35.1	1574.4 ± 40.1	0.272
SI (%)	92.4 ± 20.5	98.6 ± 19.1	0.127

negatively affect bone did not contribute to the models. The effect size of the relationships was considered moderate (BUA: $\eta p^2 = 0.088$ and SI: $\eta p^2 = 0.073$). Differences in mean SOS between antipsychotic users and non-users failed to reach statistical significance (p = 0.07) (Table 2).

4. Discussion

This study suggests antipsychotic use is associated with reduced QUS parameters. Antipsychotic users had lower BUA and SI values compared to non-users independent of age, sex, weight, alcohol intake, physical activity, smoking, SES, duration of antipsychotic use and use of other medications known to affect bone.

To our knowledge, this is the first study to investigate the association between antipsychotic use and QUS parameters in a population-based sample of adults, limiting our ability to compare directly to previous studies. However, some studies have reported similar findings for clinical samples of patients with psychosis or schizophrenia (Rey-Sanchez et al., 2009; Renn et al., 2009; Partti et al., 2010). Partti et al. found patients with affective psychosis (22.6 % used antipsychotics) and schizophrenia (68.4 % used antipsychotics) had lower BUA and SOS values than age- and sex-matched controls (Partti et al., 2010). In another study, patients with schizophrenia (n = 73, 65.7 % male) taking antipsychotics were compared with 73 age-matched controls. Women with schizophrenia had a lower amplitude-dependent speed of sound (Ad-SoS) value than controls (Rey-Sanchez et al., 2009). Lastly, in another cross-sectional study, patients with chronic schizophrenia taking antipsychotics (n = 965, 65 % male) had lower BUA values compared to controls (Renn et al., 2009). All in all, it is likely both schizophrenia and antipsychotic use are associated with reductions in QUS parameters reflecting poorer bone health.

The underlying mechanism explaining the association between antipsychotic use and reduced bone quality is not clear. Antipsychotics act to block dopamine-D2 receptors which consequently attenuates the inhibitory action of dopamine on prolactin secreted from the pituitary gland. This results in hyperprolactinemia, which may increase bone loss (Graham et al., 2011). Reduced QUS parameters have been seen in women with prolactinoma compared to healthy controls (Vartej et al., 2001). In the current study, blood hormone measurements were not available; thus, we were unable to investigate this relationship. Antidepressant medications are commonly taken alongside antipsychotics and have also been involved in bone loss and associated with lower QUS parameters (Rauma et al., 2015). Furthermore, lifestyle behaviors such as smoking and physical inactivity are recognised risk factors of lower QUS parameters (Pye et al., 2010). In this study antipsychotic users had higher rates of antidepressant use, were more likely to smoke and were less physically active compared to non-users. However, these factors were tested in our regression model, but did not explain the findings. Duration of antipsychotic use has been investigated in previous studies, with long term use related to greater reduction in bone mineralization (Naidoo et al., 2003; Cengiz et al., 2019). However, we did not detect this pattern in our study.

This study included adults from the general population selected randomly, not on the basis of disease, which is a major strength of the study. Furthermore, this design addressed the issue of confounding by indication, a commonly encountered bias in observational studies of medication effects, as no participants had a diagnosis of schizophrenia. Being able to account for several potential confounders is another strength of this study. However, we were unable to conduct subgroup analyses looking into specific antipsychotics due to small numbers. We acknowledge that findings from this study may not be generalizable to other populations outside the study region or of different ethnicity.

5. Conclusion

To conclude, this study suggests that adults taking antipsychotics have poorer bone health, as assessed by QUS. The probability of developing osteoporosis should be taken into account when antipsychotics are prescribed.

Abbreviations

BMD	Bone mineral density
BUA	Broadband ultrasound attenuation
CI	Confidence interval
DXA	Dual-energy x-ray absorptiometry
GEE	Generalized Estimating Equations

Table 2
Adjusted[a] marginal mean differences and effect sizes for antipsychotic users and non-users according to QUS parameters (BUA, SOS, SI).

	Antipsychotic users			Non-users			Contrast for mean difference				
	Mean	SE	95 % CI	Mean	SE	95 % CI	Contrast estimate (%)	SE	Wald Chi-square (df)	Partial Eta squared[b]	p
BUA	108.70	2.26	(104.26–113.14)	116.42	0.48	(115.48–117.37)	7.7	2.74	7.93 (1)	0.088	0.005
SOS	1562.69	3.77	(1555.30–1570.09)	1570.86	0.91	(1569.07–1572.65)	8.2	4.51	3.27 (1)	0.055	0.070
SI	89.92	1.55	(86.89–92.95)	97.30	0.41	(96.48–98.12)	7.4	1.93	14.51 (1)	0.073	<0.001

[a] Adjusted for age, sex, weight and two-way interactions (antipsychotics * age; antipsychotics * sex; antipsychotics * weight; age * sex).
[b] Cut offs were set as small (≥0.01), medium (≥0.06) and large (≥0.14).

GOS	Geelong Osteoporosis Study
IQR	Inter quartile range
QUS	Quantitative ultrasound
SEIFA	Socio-Economic Index for Areas
SES	Socio-economic status
SI	Stiffness index
SOS	Speed of sound
SSRI	Selective serotonin reuptake inhibitors
WHO	World Health Organization

Ethics approval and consent to participate

Ethics approval was obtained from the Human Research Ethics Committee at Barwon Health (ID 92/01 and 00/56). All participants provided informed, written consent.

Human and animal rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Behnaz Azimi Manavi: Writing – original draft, Formal analysis. **Mohammadreza Mohebbi:** Formal analysis. **Amanda L. Stuart:** Writing – review & editing. **Julie A. Pasco:** Methodology, Supervision, Writing – review & editing. **Jason M. Hodge:** Writing – review & editing. **D. Kavindi Weerasinghe:** Writing – review & editing. **Rasika M. Samarasinghe:** Writing – review & editing. **Lana J. Williams:** Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

BAM, MM, ALS, JAP, JMH, DKM, RMS and LJW declare they have no conflicts of interest.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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