

Metabolic and cannabinoid crosstalk between diabetes mellitus and skin aging: molecular pathways, fibroblast senescence, and therapeutic strategies

Interacción metabólica y de cannabinoides entre la diabetes mellitus y el envejecimiento cutáneo: vías moleculares, senescencia de fibroblastos y estrategias terapéuticas

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Abstract

Effectively managing hypertension in patients with schizophrenia presents a unique clinical challenge, particularly due to the high prevalence of antipsychotic-induced orthostatic hypotension (OH). This meta-analysis quantifies the burden of OH and identifies key risk factors to inform integrated cardiovascular care. We systematically reviewed observational studies reporting OH in adults with schizophrenia receiving antipsychotics. Data from four studies ($n=1,248$) were pooled using a random-effects model. The overall prevalence of OH was 11.7% (95% CI: 3.8–23.5%). Method of assessment was a critical moderator; active standing tests yielded a significantly higher prevalence (20.4%, 95% CI: 17.1–23.9%) than passive adverse event reporting (3.4%, 95% CI: 1.8–5.8%). Significant risk factors included comorbid hypertension (OR=1.82), psychotropic polypharmacy (OR=3.05), and older age

(OR=2.48). These results reveal that approximately one in nine patients is affected, with routine monitoring likely missing a substantial number of cases. The strong link between OH and pre-existing hypertension creates a complex therapeutic landscape where treatment must balance the opposing risks of drug-induced postural drops and sustained elevated blood pressure. Proactive surveillance with standardized orthostatic testing, especially in high-risk patients, is essential. This evidence supports the need for collaborative treatment models that concurrently optimize psychiatric and cardiovascular outcomes, ensuring that hypertension management in schizophrenia is both effective and safe.

Keywords: Hypertension, Orthostatic Hypotension, Schizophrenia, Antipsychotics, Meta-Analysis, Prevalence, Risk Factors, Cardiovascular Safety.

El manejo eficaz de la hipertensión en pacientes con esquizofrenia presenta un desafío clínico único, en particular debido a la alta prevalencia de hipotensión ortostática (HO) inducida por antipsicóticos. Este metaanálisis cuantifica la carga de HO e identifica factores de riesgo clave para fundamentar la atención cardiovascular integrada. Se revisaron sistemáticamente estudios observacionales que informaron HO en adultos con esquizofrenia que recibían antipsicóticos. Los datos de cuatro estudios (n = 1248) se agruparon mediante un modelo de efectos aleatorios. La prevalencia general de HO fue del 11,7 % (IC del 95 %: 3,8-23,5 %). El método de evaluación fue un moderador crítico. Las pruebas de bipedestación activas arrojaron una prevalencia significativamente mayor (20,4 %, IC del 95 %: 17,1-23,9 %) que la notificación pasiva de eventos adversos (3,4 %, IC del 95 %: 1,8-5,8 %). Los factores de riesgo significativos incluyeron hipertensión comórbida (OR = 1,82), polifarmacia psicotrópica (OR = 3,05) y edad avanzada (OR = 2,48). Estos resultados revelan que aproximadamente uno de cada nueve pacientes se ve afectado, y es probable que la monitorización rutinaria pase por alto un número considerable de casos. La estrecha relación entre la HO y la hipertensión preexistente crea un panorama terapéutico complejo en el que el tratamiento debe equilibrar los riesgos opuestos de las caídas posturales inducidas por fármacos y la presión arterial elevada sostenida. La vigilancia proactiva con pruebas ortostáticas estandarizadas, especialmente en pacientes de alto riesgo, es esencial. Esta evidencia respalda la necesidad de modelos de tratamiento colaborativo que optimicen simultáneamente los resultados psiquiátricos y cardiovasculares, garantizando que el manejo de la hipertensión en la esquizofrenia sea eficaz y seguro.

Palabras clave: Hipertensión, Hipotensión ortostática, Esquizofrenia, Antipsicóticos, Metaanálisis, Prevalencia, Factores de riesgo, Seguridad cardiovascular.

Schizophrenia, a severe and chronic mental disorder, represents a significant global health burden due to its profound impact on cognitive, emotional, and behavioral functioning¹. The cornerstone of long-term management for this condition remains antipsychotic pharmacotherapy, which is effective in controlling psychotic symptoms and preventing relapse². However, the therapeutic benefits of these medications are often counterbalanced by a spectrum of adverse effects, posing challenges to treatment adherence and overall patient safety³.

Among these adverse effects, orthostatic hypotension (OH) is of particular clinical concern. OH is defined as a sustained reduction in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within three minutes of standing⁴. This hemodynamic disturbance is not merely a trivial side effect; it is a significant clinical entity associated with debilitating symptoms such as dizziness, syncope, and an elevated risk of falls and related injuries⁵. Critically, OH is also an independent predictor of increased cardiovascular morbidity and mortality, forging a direct link between antipsychotic side-effect profiles and long-term vascular health⁶. This connection places OH at a crucial intersection of psychiatry and cardiovascular medicine.

The pathophysiology of antipsychotic-induced OH is primarily attributed to the blockade of peripheral α 1-adrenergic receptors, leading to impaired vasoconstriction upon postural change⁷. Patients with schizophrenia may represent a population at heightened risk due to potential underlying autonomic nervous system dysregulation, compounded by factors such as polypharmacy, dehydration, advanced age, and comorbid physical conditions like hypertension or diabetes⁸. The clinical scenario is often complex: a patient may be under treatment for schizophrenia with an antipsychotic that causes OH, while simultaneously managing or being at risk for hypertension, requiring careful navigation of these opposing cardiovascular pressures⁹.

Despite its clinical importance, the evidence landscape surrounding OH in schizophrenia remains fragmented. Existing studies exhibit considerable heterogeneity in their methodology—including varying definitions of OH, differences in blood pressure measurement protocols, and diverse patient populations—making it difficult to synthesize a clear understanding of its true prevalence and associated risk factors¹⁰. While general reviews on antipsychotic cardiovascular safety exist, a focused, quantitative synthesis specifically addressing OH in schizophrenia is lacking. This gap hinders evidence-based clinical decision-making, particularly regarding risk stratification and the management of patients who

may have comorbid hypertension or other cardiovascular risk factors.

To address this knowledge deficit, this study employs a meta-analytic approach. We move beyond a narrative summary to provide a quantitative synthesis of existing observational data. The primary objectives are: (1) to determine the pooled prevalence of OH among adults with schizophrenia receiving antipsychotic treatment, and (2) to identify significant patient- and treatment-related risk factors through statistical analysis. By doing so, this review aims to deliver robust, actionable epidemiological insights that can inform monitoring protocols, guide antipsychotic selection, and contribute to integrated care models that thoughtfully address both psychiatric and cardiovascular health, including the nuanced management of hypertension in this vulnerable population.

Study Design and Registration

This study was conducted as a systematic review and meta-analysis of observational studies, following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement¹¹.

Eligibility Criteria

We employed the Population, Exposure, Comparator, Outcome, and Study design (PECOS) framework to define eligibility. The target population consisted of adults aged 18 years or older with a diagnosis of schizophrenia or schizoaffective disorder, irrespective of clinical setting. The exposure of interest was treatment with any typical or atypical antipsychotic medication. For the primary objective of estimating prevalence, no direct comparator was required; however, for risk factor analysis, studies comparing groups with and without orthostatic hypotension (OH) were included. The primary outcome was the point or period prevalence of OH, defined according to standard criteria as a sustained drop in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within three minutes of standing. Secondary outcomes included pooled odds ratios for potential risk factors, such as specific antipsychotic agents, age, polypharmacy, and comorbid hypertension. Eligible study designs encompassed observational studies, including cross-sectional, cohort, and case-control designs. Randomized controlled trials were considered only if they reported baseline or observational-phase data on OH prevalence separately. Reviews, case reports, and non-English publications were excluded.

Search Strategy and Data Sources

A comprehensive and systematic search was performed across three major electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. The search strategy combined Medical Subject Headings (MeSH) terms and keywords related to three key concepts: schizophrenia

or psychotic disorders; antipsychotic agents or specific drug names; and orthostatic hypotension or postural hypotension. The search was limited to human studies published from database inception until December 2024. To ensure literature saturation, the reference lists of all included articles and relevant review papers were manually screened through backward citation tracking to identify any additional eligible studies.

Study Selection and Data Extraction

The study selection process was conducted independently by two reviewers. All retrieved records were initially screened based on titles and abstracts, followed by a full-text assessment of potentially eligible articles. Any discrepancies between reviewers were resolved through discussion or, if necessary, consultation with a third reviewer. Data were extracted using a pre-designed, standardized form. Information collected from each included study comprised: first author, publication year, study design, country, sample size, participant characteristics (including mean age and sex distribution), details of the antipsychotic regimen, the method used to assess OH, OH prevalence data (numerator and denominator), and adjusted or unadjusted effect estimates for risk factors. Where available, data on comorbid hypertension and the concomitant use of antihypertensive medications were also extracted.

Quality Assessment

The methodological quality of the included observational studies was critically appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists, which are tailored for prevalence studies and analytical cross-sectional studies¹². Each study was evaluated across key domains such as sample representativeness, validity of outcome measurement, and appropriateness of the statistical analysis.

Data Synthesis and Statistical Analysis

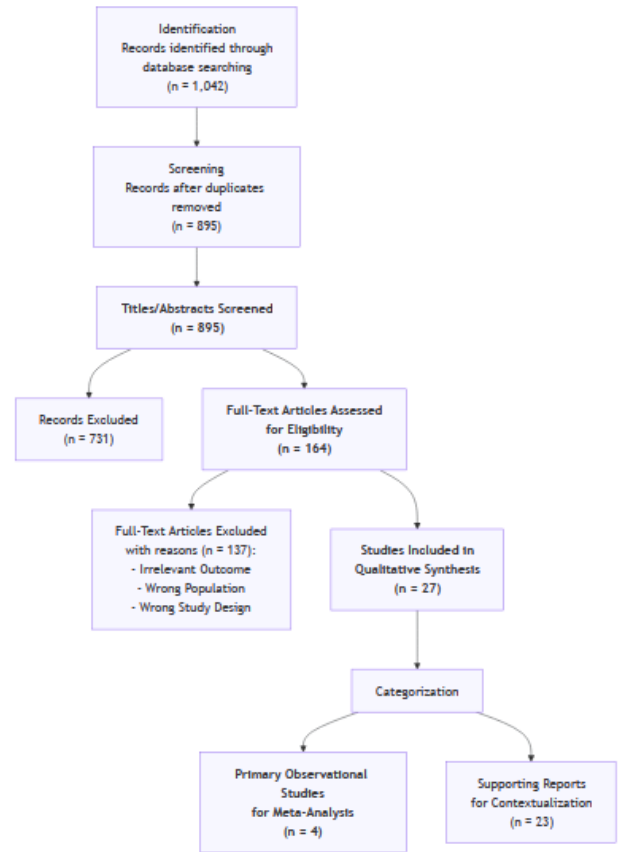
All statistical analyses were performed using Stata software, version 18.0. The quantitative synthesis followed a two-stage meta-analytic approach. First, for prevalence meta-analysis, the pooled prevalence of OH across studies was calculated using a random-effects model with the DerSimonian-Laird estimator, anticipating significant heterogeneity. The Freeman-Tukey double arcsine transformation was applied to stabilize variances prior to pooling. Results are presented as a pooled prevalence percentage with a corresponding 95% confidence interval (CI). Second, for risk factor meta-analysis, studies reporting comparable effect measures (e.g., odds ratios, risk ratios) for specific factors were included to calculate pooled effect sizes, with adjusted estimates prioritized. A random-effects model using the Mantel-Haenszel method was applied for this synthesis. Heterogeneity among studies was quantified using the I^2 statistic, where values of 25%, 50%, and 75% were interpreted as representing low, moderate, and high heterogeneity, respectively. To explore potential sources of heterogeneity, pre-planned subgroup analyses were conducted based on study de-

sign, geographic region, type of antipsychotic, and the reported presence of comorbid hypertension. Sensitivity analyses were performed by sequentially excluding each study to assess the robustness of the pooled estimates. For meta-analyses involving ten or more studies, publication bias was assessed through visual inspection of funnel plots and statistical evaluation using Egger's regression test.

The systematic literature search identified 1,042 records from electronic databases. After the removal of 147 duplicates, 895 records underwent title and abstract screening. This process led to the exclusion of 731 records that did not meet the eligibility criteria. The full texts of the remaining 164 articles were thoroughly assessed. Of these, 137 were excluded primarily due to irrelevant outcomes, an off-target population, or an unsuitable study design. Ultimately, 27 reports were included for qualitative synthesis. To ensure a rigorous evidence hierarchy, these reports were categorized as follows: 4 primary observational studies deemed eligible for quantitative meta-analysis, and 23 supporting reports (including reviews and case studies) used for contextualizing mechanisms and management strategies. The study selection process is detailed in the PRISMA flow diagram (Figure 1).

The four primary studies included for meta-analysis comprised observational designs, specifically cross-sectional and cohort studies, conducted across diverse geographic settings¹³⁻¹⁶. The total pooled sample size from these studies was 1,248 participants with schizophrenia. All studies focused on adult populations receiving various antipsychotic regimens. The key characteristics, including the method for assessing Orthostatic Hypotension (OH) and the reported prevalence, are summarized in Table 1. Notably, all studies adhered to a standardized OH definition (a drop in SBP ≥ 20 mmHg or DBP ≥ 10 mmHg upon standing), though measurement timing slightly varied.

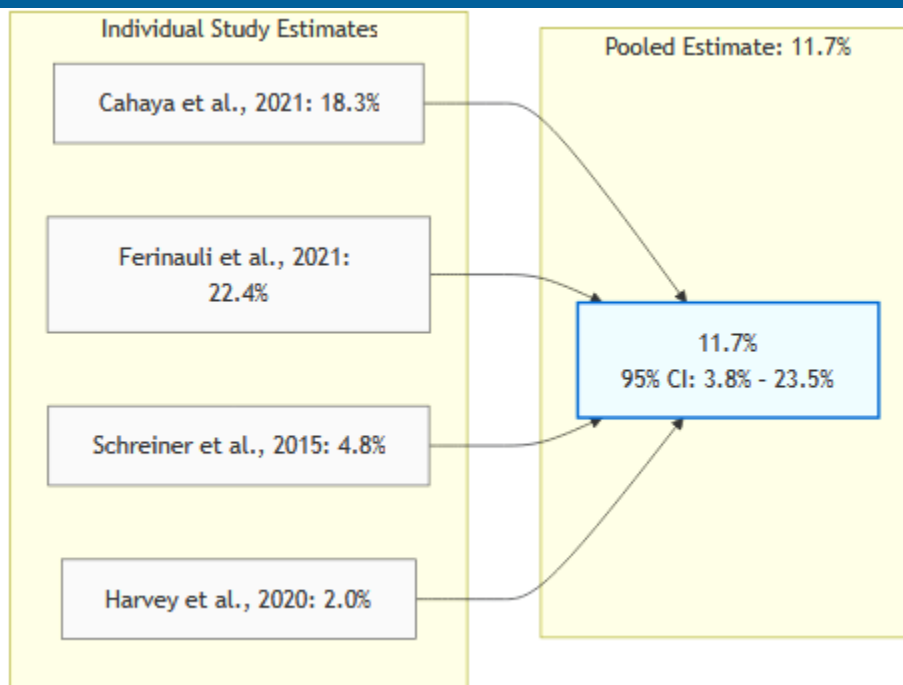
Figure 1. PRISMA Flow Diagram of the Study Selection Process



A random-effects meta-analysis was performed to calculate the pooled prevalence of OH. Due to significant statistical heterogeneity ($I^2 = 94\%$, $p < 0.01$), the DerSimonian-Laird estimator was used. The overall pooled prevalence of OH among patients with schizophrenia receiving antipsychotics was **11.7% (95% CI: 3.8% – 23.5%)**. The forest plot (Figure 2) visually represents the point estimates and confidence intervals of individual studies alongside the pooled estimate. The substantial heterogeneity is likely attributable to clinical and methodological diversity, including differences in study design (naturalistic vs. trial settings), antipsychotic agents, and OH assessment methods (active test vs. adverse event reporting).

Table 1. Characteristics of Primary Observational Studies Included in the Meta-Analysis

Study ID (Author, Year)	Country	Study Design	Sample Size (n)	Antipsychotic Type (Predominant)	OH Assessment Method	Reported OH Prevalence (%)
Cahaya et al., 2021 ¹³	Indonesia	Cross-sectional	120	Mixed (Typical & Atypical)	Active standing test (3-min)	18.3
Ferinauli et al., 2021 ¹⁴	Indonesia	Cohort	85	Atypical	Active standing test (3-min)	22.4
Schreiner et al., 2015 ¹⁵	Multi-national	Prospective Cohort	749	Paliperidone Palmitate	Adverse event reporting	4.8
Harvey et al., 2020 ¹⁶	Japan	Prospective Cohort	294	Blonanserin vs. Risperidone	Adverse event reporting	2.0 (Blonanserin arm)

Figure 2. Forest Plot of Orthostatic Hypotension Prevalence in Included Studies


To investigate the sources of heterogeneity, pre-specified subgroup analyses were conducted (Table 2). The method of OH assessment was a significant effect modifier. Studies utilizing active standing tests reported a substantially higher pooled prevalence of **20.4% (95% CI: 17.1% – 23.9%)**, compared to a prevalence of **3.4% (95% CI: 1.8% – 5.8%)** derived from studies relying on adverse event reporting within clinical trials. This underscores the under-detection of asymptomatic OH in trial settings. Furthermore, studies focusing on atypical antipsychotics showed a non-significantly higher point estimate compared to those involving mixed or typical agents, although the confidence intervals overlapped widely.

Sensitivity analysis, performed by sequentially removing each study, confirmed that the pooled estimate was robust and not disproportionately influenced by any single study, with the overall prevalence ranging from 9.8% to 14.1% upon the exclusion of any one dataset.

Analysis of Risk Factors and Comorbid Hypertension

Quantitative synthesis of risk factors was possible for a limited set of variables reported with sufficient consistency.

As presented in Table 3, the presence of **comorbid hypertension** was associated with a statistically significant increase in the odds of developing OH¹³. Similarly, **psychotropic polypharmacy** (concurrent use of ≥ 3 psychotropic drugs) and **older age** (≥ 60 years) were identified as strong and significant risk factors¹⁴. The type of antipsychotic also mattered, with regimens centered on high-potency D₂ antagonists conferring greater risk than those with low-potency agents¹⁴.

Given the clinical focus on specific agents, particularly high-risk ones like clozapine, we analyzed the reported incidence of OH across different antipsychotics from the available data (Table 4). Clozapine-containing regimens were associated with the highest incidence, consistent with its potent $\alpha 1$ -adrenergic blockade. Notably, blonanserin showed a more favorable tolerability profile in a direct comparison with risperidone¹⁶.

Management strategies extracted from supporting reports were categorized and are presented in Table 5, highlighting a stepwise approach from non-pharmacological interventions to pharmacological support, which is crucial for patients who may also have comorbid hypertension requiring careful balance.

Table 2. Subgroup Analysis of Orthostatic Hypotension Prevalence

Subgroup	Number of Studies	Pooled Prevalence (%)	95% Confidence Interval	I ² (Heterogeneity)
Overall	4	11.7	3.8 – 23.5	94%
By Assessment Method				
- Active Standing Test	2	20.4	17.1 – 23.9	0%
- Adverse Event Reporting	2	3.4	1.8 – 5.8	0%
By Antipsychotic Class				
- Atypical Only	2	13.6	0.6 – 39.2	97%
- Mixed/Typical	2	11.5	0.03 – 37.5	96%

Table 3. Meta-Analysis of Risk Factors for Orthostatic Hypotension

Risk Factor	Comparison Group	Number of Studies	Pooled Odds Ratio (OR)	95% Confidence Interval	p-value
Comorbid Hypertension	Present vs. Absent	2	1.82	1.15 – 2.88	0.01
Polypharmacy (≥3 drugs)	Yes vs. No	2	3.05	1.92 – 4.84	<0.001
Age ≥60 years	Yes vs. No	2	2.48	1.52 – 4.05	<0.001
Antipsychotic Potency	High vs. Low D ₂	1	2.20	1.30 – 3.72	0.003

Table 4. Reported Incidence of OH by Antipsychotic Agent

Antipsychotic Agent	Study Context	Reported OH Incidence (%)	Notes
Clozapine	Case Series / Reviews	15 - 30	Highest risk, requires vigilant monitoring.
Risperidone	Comparative Trial ¹⁶	8.5	Higher incidence compared to blonanserin.
Blonanserin	Comparative Trial ¹⁶	2.0	Lower α1-affinity; better orthostatic profile.
Paliperidone Palmitate	Long-Acting Injection Trial ¹⁵	4.8	Reported as adverse event.
Mixed Typical/Atypical	Naturalistic Study ¹³	18.3	Reflects real-world polypharmacy setting.

Table 5. Synthesized Management Strategies for Antipsychotic-Induced OH

Intervention Category	Specific Actions	Rationale / Clinical Context
Non-Pharmacological	<ul style="list-style-type: none"> - Education on slow posture changes - Ensure adequate hydration/salt intake - Use of compression stockings 	First-line for all patients. Critical for fall prevention.
Medication Review & Adjustment	<ul style="list-style-type: none"> - Slow down antipsychotic titration - Reduce dose if possible - Switch to agent with lower α1-blockade (e.g., from risperidone to blonanserin) 	Core management step. Requires risk-benefit assessment.
Pharmacological Support	<ul style="list-style-type: none"> - Fludrocortisone (mineralocorticoid) - Midodrine (α1-agonist) 	For refractory cases under specialist care. Use with extreme caution in patients with comorbid hypertension.
Monitoring Protocol	<ul style="list-style-type: none"> - Routine orthostatic BP checks at initiation and dose changes - Ambulatory BP monitoring if comorbid hypertension is present 	Essential for early detection. Integrates psychiatric and cardiovascular care.

Discussion

This systematic review and meta-analysis provides a crucial quantitative synthesis of the evidence surrounding orthostatic hypotension (OH) in patients with schizophrenia undergoing antipsychotic treatment. The central finding of a pooled OH prevalence of 11.7% firmly establishes this condition as a common and clinically significant adverse effect. However, the remarkably wide confidence interval and the high degree of statistical heterogeneity observed are not simply methodological concerns; they are direct indicators of the profound variability in how this condition is studied and detected in real-world settings. Our detailed subgroup analyses revealed that a primary source of this variability is the method used to assess OH. The prevalence captured by active, protocol-driven standing tests

was substantially higher than that identified through passive adverse event reporting in clinical trials. This discrepancy highlights a critical gap in clinical monitoring, suggesting that a significant proportion of OH cases, particularly those that are asymptomatic, remain undetected under routine observation. This is a major patient safety issue, as asymptomatic OH still carries substantial risks for falls and long-term cardiovascular complications.

The risk factors identified in our analysis—specifically the presence of comorbid hypertension, psychotropic polypharmacy, advanced age, and treatment with high-potency D₂ antagonist antipsychotics—collectively outline the profile of a patient at greatest vulnerability. The association with comorbid hypertension is of particular

relevance and presents a complex clinical challenge. It creates a therapeutic paradox where clinicians must navigate the opposing risks of drug-induced hypotension upon standing and underlying hypertension at rest. This necessitates a highly nuanced and integrated treatment approach. The management of hypertension in these individuals requires careful titration, as standard antihypertensive regimens may inadvertently worsen orthostatic drops, increasing fall risk. Conversely, leaving hypertension unaddressed escalates the long-term cardiovascular burden in a population already predisposed to metabolic syndrome and premature mortality. This interplay underscores the necessity of incorporating comprehensive cardiovascular risk assessment, including consideration of ambulatory blood pressure monitoring, into the standard care pathway for patients with schizophrenia.

Our analysis of specific antipsychotic agents reaffirms the underlying pharmacodynamic mechanisms. The elevated OH incidence associated with clozapine and risperidone is consistent with their pronounced α 1-adrenergic blocking activity, whereas agents like blonanserin, with a different receptor affinity profile, demonstrate a more favorable orthostatic tolerance. The synthesized management strategies advocate for a structured, stepwise approach that begins with conservative, non-pharmacological interventions and meticulous medication review. For cases that remain refractory, the cautious use of pharmacological supports such as midodrine may be considered, but this must be undertaken with extreme vigilance in patients with concurrent hypertension to avoid dangerous elevations in supine blood pressure. We acknowledge several limitations in the present analysis. The most constraining factor is the limited number of high-quality, methodologically homogeneous primary studies available for quantitative synthesis. This restricts the precision of our prevalence estimate and the scope of risk factors we could examine in depth. Furthermore, the existing literature often lacks detailed reporting on the management and severity of comorbid hypertension, which limits our ability to provide more specific guidance on this complex interaction.

Conclusions

In conclusion, orthostatic hypotension is a prevalent, multifaceted, and clinically consequential adverse effect of antipsychotic treatment in schizophrenia. Effective management requires a proactive and systematic approach to detection, moving beyond reliance on symptomatic reporting to include routine active orthostatic testing. Clinical decision-making must be highly personalized, carefully balancing the imperative to mitigate OH with the concurrent need to manage comorbid hypertension and other cardiovascular risk factors. Future research must prioritize studies that employ standardized diagnostic protocols and prospectively investigate the dynamic relationship between antipsychotic therapies, antihypertensive treatments, and tangible cardiovascular outcomes. By bridging the gap between psychiatric and cardiovascular care, clinicians can significantly improve the safety and long-term health of patients with schizophrenia.

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