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Benzodiazepine use in schizophrenia: A review of the literature

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Abstract

Introduction: Emerging data suggest that benzodiazepines are not appropriate for patients in the long-term management of schizophrenia.

Methods: A literature search was conducted on studies published on the topic of benzodiazepines and schizophrenia from 2004 to 2024. The search returned more than 3000 results of which 27 were relevant to include in this scoping review.

Results: The publications identified for this review spanned benzodiazepines' negative impact on mortality, hospitalizations, brain volume changes, cognition, global functioning, and quality of life. There were also publications identified to evaluate the current evidence for use in schizophrenia as well as related conditions, such as tardive dyskinesia, akathisia, and catatonia.

Discussion: Based on the currently available guidelines, there seems to be a lack of a clear stance against the regular use of benzodiazepines in schizophrenia. These organizations should be more straightforward about the specific potential uses and risks associated with benzodiazepine use in schizophrenia.

Keywords: schizophrenia, benzodiazepines

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Introduction

Schizophrenia is a chronic mental health disorder characterized by positive, negative, and cognitive symptoms. Due to the complexity of the illness, the wide variation in symptoms, and the treatment-resistant presentation in many patients, polypharmacy is a common practice.[1] Oftentimes, more than one antipsychotic is used; additionally, antidepressants, mood stabilizers, and benzodiazepines (BZDs) are commonly prescribed along with antipsychotics. Some emerging evidence supports the use of more than one antipsychotic.[2] However, other data suggest that BZDs may not be appropriate for this patient population.[1] This paper reviews the literature on the safety and efficacy of BZDs when used in patients with schizophrenia.

Methods

We systematically searched PubMed for "schizophrenia AND benzodiazepines" (English-language, January 1, 2004–June 15, 2024). Two reviewers independently screened titles/abstracts and full texts; disagreements were resolved by consensus. Articles were included if they examined BZD use in individuals with schizophrenia or related psychotic disorders, including schizophrenia spectrum or psychosis spectrum disorders. Studies that included mixed psychiatric populations were included only if data for schizophrenia-related diagnoses could be reasonably extracted or if the sample predominantly consisted of individuals with psychotic disorders. Editorials,

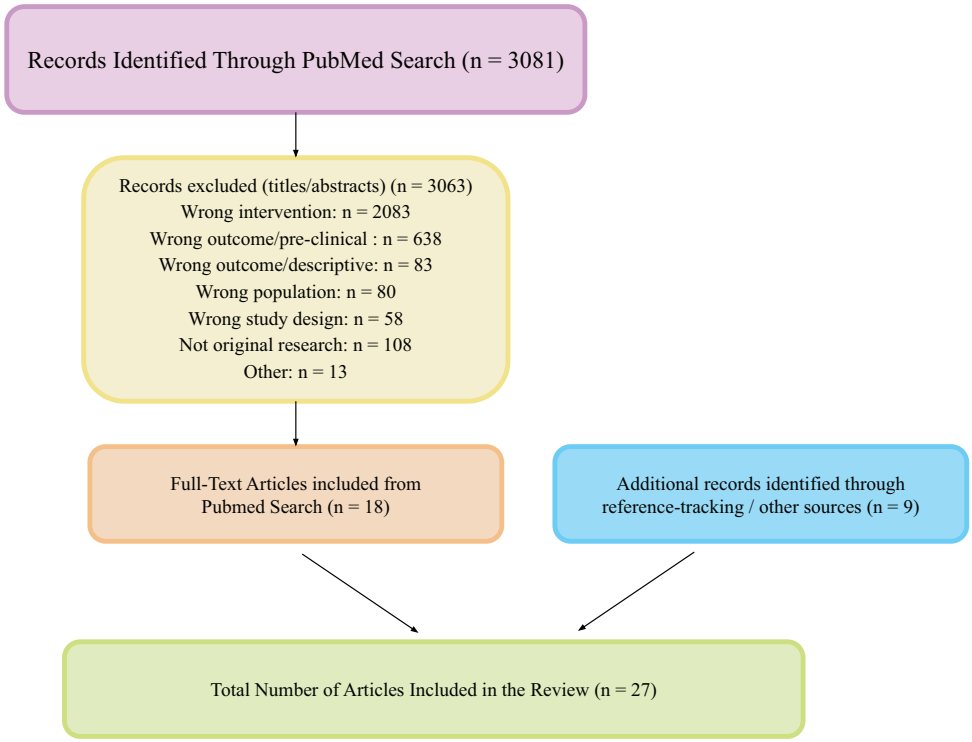

FIGURE: Records identified through PubMed search (*n* = 3081)

opinion pieces, uncontrolled case series, and studies without BZD-specific outcomes were excluded.

Results

The search yielded 3081 records. After screening, 27 studies met inclusion criteria (9 controlled trials, 5 systematic reviews/meta-analyses, 8 cohort or case-control studies, 5 cross-sectional). The Figure presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection.

Mortality

Several studies identify an association between BZD use in schizophrenia and increased mortality, beginning with a 2010 Danish population-level study.[3] The objective of the study was to investigate if polypharmacy was associated with excess mortality from natural causes in schizophrenia. Current drug use was defined as at least 1 prescription filled within 90 days before the date of death or the index date. Using a high-quality national registry, this study analyzed 27 633 patients with schizophrenia aged 18 to 53 years. In the patients included, there were 193 natural deaths over a 2-year period (suicide, homicide, accidental, or unknown causes were excluded). The authors then identified 1937 age- and sex-matched controls. Compared with antipsychotic monotherapy, the number of antipsychotics used did not increase mortality risk (no antipsychotics: adjusted odds ratio [aOR] 1.48, 95% CI, 0.89-2.46; 2 antipsychotics: aOR 0.91, 95% CI, 0.61-1.36; 3 or more antipsychotics: aOR 1.16, 95% CI, 0.68-2.00). However, current use of a BZD with a long half-life (ie, diazepam, chlordiazepoxide, clobazam, nitrazepam, flunitrazepam, and clonazepam) was associated with increased risk of death versus patients who had no BZD exposure (aOR 1.78, 95% CI, 1.25-2.52).

In a nationwide Finnish cohort of 2588 adults hospitalized for first episode schizophrenia, current BZD exposure was associated with higher all-cause mortality compared with periods of no BZD use during a mean 4.2-year follow up that began at discharge: adjusted hazard ratio (aHR) 1.91, 95% CI 1.13-3.22.[4] Exposure to BZDs was calculated as person-years and derived from pharmacy fills. Mortality rates per 1000 person-years varied and was highest for temazepam (30.9), diazepam (30.3), and oxazepam (29.2). Excess risk was evident for both suicide deaths (HR 3.83, 95% CI 1.45-10.12 versus no BZD use) and nonsuicide deaths (HR 1.60, 95% CI 0.86-2.97 versus no BZD use).

A Swedish study of 21 492 patients with schizophrenia followed over 5 years categorized exposure to antipsychotics, antidepressants, and BZDs by defined daily doses (DDD).[5] This study was unique in that it separated exposure by DDD into 4 categories: no exposure (0 DDD), low (>0 to 0.5 DDDs), moderate (0.5 to 1.5), and high (>1.5 DDD). Time-dependent Cox models that controlled for concurrent exposure to the other 2 drug classes as well as

demographic and clinical covariates, showed that moderate antipsychotic use reduced all-cause mortality by 41% (HR 0.59, 95% CI 0.49-0.70, $p < 0.001$) and high use by 25% (HR 0.75, 95% CI 0.63-0.89, $p = 0.001$). Moderate and high antidepressant exposure lowered mortality by 15% (HR 0.85, 95% CI 0.73-0.98, $p = 0.031$) and 29% (HR 0.71, 95% CI 0.59-0.86, $p < 0.001$), respectively. Low-dose BZDs were neutral (HR 1.04, 95% CI 0.92-1.18, $p = 0.54$), but moderate and high BZD exposure increased mortality by 23% (HR 1.23, 95% 1.10-1.37, $p < 0.001$) and 74% (HR 1.74, 95% 1.50-2.03, $p < 0.001$), respectively. Each hazard ratio reflects the independent effect of that specific medication exposure after adjustment for concurrent psychotropic use.

The first US study (and first study outside of the Nordic region in Europe) on this topic used Ohio Medicaid Claims data to follow 18 953 patients with schizophrenia for 6 years who were aged 18 to 58 years old.[6] The data showed that mortality rates were higher for the 3467 (18.3%) who were prescribed a BZD without an antipsychotic and for the 1736 (9.2%) who were prescribed a BZD with an antipsychotic; mortality was 208% (HR 3.08, 95% CI 2.63-3.61, $P < 0.001$) and 48% (HR 1.48, 95% CI 1.15-1.91, $P = 0.002$) higher, respectively, compared with those not taking BZDs. The increased risk of death was attributable to suicide, accidental poisoning, and natural causes.

A second Swedish study was the most recent publication to investigate this association.[7] The defining feature of this study was that it evaluated patients with a first hospitalization for psychosis between the ages of 16 and 25 ($n = 2488$). Cases were followed for 5 years after hospital discharge, and the cumulative mortality was found to be 3.9% (suicide mortality 2.4%). During periods of BZD exposure, patients showed nearly threefold higher risk of suicide (HR 3.01, $p = 0.0018$) and of death from other causes (HR 3.26, $p = 0.0098$) relative to their own BZD-free periods.[7]

Hospital-Acquired Pneumonia

Hospital-acquired pneumonia (HAP) risk in inpatients with schizophrenia was evaluated in 2 large retrospective cohorts that focused on BZD exposure. In a Taiwanese nested case-control study of 34 929 psychiatric admissions, Cheng et al[8] report that current use of midazolam (aOR 6.56), diazepam (= 3.43), lorazepam (= 2.16) and triazolam (= 1.80) independently increased HAP risk versus nonusers, with a clear dose-response across diazepam-equivalent categories. A single-center Chinese study by Yang et al,[9] employing propensity score matching in 7085 psychiatric admissions, found that any BZD use conferred an increased risk for HAP (aOR 3.13) versus nonusers after adjustment for antipsychotic regimen, demographics, and comorbidity.

Hospitalizations

A Norwegian cohort study followed 663 patients with schizophrenia for 10 years posthospital discharge to assess the impact of various medications on readmission rates due to overactive, aggressive, disruptive, or agitated behavior (OADA).[10] Medications prescribed were assessed retrospectively using medical records, and adherence was evaluated using additional information from patients, families, and serum-concentration measurements when available. During the 10-year postdischarge follow-up, 161 of the 663 patients (24.3%) were rehospitalized with OADA at a median of 2.1 years (mean ± SD = 2.8 ± 2.6 years) after their index discharge. Use of antipsychotics reduced the risk of OADA-related readmission by 67% (aHR 0.33, $p < 0.01$) and antidepressants by 43% (aHR 0.57, $p = 0.03$), whereas BZDs increased the risk by 95% (aHR 1.95, $p < 0.01$); mood stabilizers had no significant effect.

A Japanese study tracked 108 patients with schizophrenia discharged from a hospital who had continuous treatment in an outpatient clinic for at least 2 years to investigate the relationship between BZD use and rehospitalizations.[11] During the 2-year postdischarge follow-up, 44 of the 108 patients (40.7%) were rehospitalized; high-dose BZD prescribed at discharge (≥10 mg/day diazepam-equivalent) versus no BZD increased the rehospitalization risk more than sixfold (HR 6.54, $p = 0.011$); low-dose BZD (<10 mg/day diazepam-equivalent) was not associated with earlier readmission.

Brain Volume

The first study reporting structural brain changes related to BZD use in schizophrenia, published in 2017, used data from the Northern Finland Birth Cohort 1966 (NFBC1966).[12] This cohort was originally established to study the effects of preterm birth and intrauterine growth retardation on children born in 1966. However, the specific study in question examined a subset of individuals from this cohort who later developed schizophrenia. Brain MRI scans were performed on participants with schizophrenia ($n = 38$) and control participants ($n = 69$) at ages 34 and 43 to assess structural changes associated with BZD use. Over 9 years, higher antipsychotic doses were linked to increased lateral ventricle volume, whereas higher BZD doses correlated with decreased caudate nucleus volume after controlling for other medications and PANSS total scores.

A subsequent analysis of the same data set revealed that lifetime cumulative BZD doses did not correlate with brain volume changes at age 43 after controlling for antipsychotic doses in patients with schizophrenia ($n = 44$).[13] However, in patients with affective psychoses ($n = 19$), cumulative BZD doses were associated with increased total gray matter and hippocampus volumes after adjusting for confounders. This discrepancy might stem from the differences in DDD that patients took every day for a year (DDDy) between the groups: patients with schizophrenia had higher antipsychotic

usage (average DDDy = 20.1) compared with those with affective psychoses (average DDDy = 3.8) relative to their BZD use (average DDDy = 9.1 and 5.8, respectively).

Cognition/Global Functioning/Quality of Life

Several studies explore the impact of BZDs on cognitive function in schizophrenia, starting with a 2013 Japanese discontinuation study.[14] This study included 30 patients with schizophrenia who were taking second generation antipsychotics (SGAs) and BZDs for at least 3 months. Cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) before and 4 weeks after tapering off BZDs. The results showed significant improvements in verbal memory, working memory, and the composite score. Additionally, improvements were noted in the motivation/energy score on the Schizophrenia Quality of Life Scale–Japanese language version as well as in negative symptoms and total PANSS scores.

In a 24-week, double-blind Danish trial, 80 outpatients with schizophrenia or bipolar disorder who had taken BZDs for ≥3 months were instructed to taper their BZD dose by 10% to 20% every 2 weeks when receiving once-daily prolonged-release melatonin (2 mg) or matched placebo initiated concurrently with the taper and continued for the full 24 weeks.[15] Cognitive performance (using the BACS), subjective well-being (using the World Health Organization–Five Well-Being Index and the Subjective Well-Being Under Neuroleptic Treatment Scale, Short Version) and psychosocial functioning (using the Personal and Social Performance scale) were assessed at baseline, week 8, week 16, and week 24. Mean BZD dose had fallen by ∼50% by week 8, and about 43% of participants had completely discontinued BZDs by the week-24 endpoint; the rest were on markedly lower doses. BZD taper produced significant improvements in all BACS domains except motor speed, whereas melatonin conferred no additional benefit; subjective well-being and psychosocial functioning remained stable throughout.

The French FondaMental Academic Centers of Expertise for Schizophrenia cohort provided data on 407 stabilized (and on stable doses of medication for at least 3 months) community-dwelling patients with schizophrenia, 30% of whom had been taking BZDs daily.[16] This study found that daily BZD users were more likely to have impaired attention/working memory (OR 0.60, 95% CI 0.42-0.86, $p = 0.005$) versus nonusers. Verbal and performance IQ were also negatively impacted in BZD users (OR 0.98, 95% CI 0.96-0.99, $p = 0.016$ and OR 0.98, 95% CI 0.97-0.99, $p = 0.034$, respectively).

Using data from the NFBC1966, another study examined the lifetime use of psychiatric medications and cognitive function at 43 years of age in 60 individuals with schizophrenia spectrum disorders.[17] The study found no association between lifetime cumulative DDDy of BZDs and global cognition. The exposure levels to BZDs were relatively low with an average of 0.25 DDDy.

In Serbia, an exploratory analysis of 55 patients with psychosis spectrum disorder compared long-term BZD users (6 months or more) to other BZD users.[18] Long-term users exhibited lower global and cognitive functioning ($p < 0.01$), higher Brief Psychiatric Rating Scale scores (1.86 versus 1.58, $p < 0.01$), and a greater number of daily psychotropic drugs (median: 4 versus 2, $p < 0.01$).

In 101 older, long-stay Japanese inpatients with schizophrenia (average age ≈ 63 years), investigators evaluated whether 5 medication categories affected generic quality of life (EQ-5D-3L): current BZD use, antipsychotic class (FGA versus SGA), total antipsychotic dose, anticholinergic use, and mood-stabilizer use.[19] After adjusting for age, symptom severity, and side-effect scales, only BZD use showed a significant association with poorer quality of life (standardized $\beta = -0.203$, $p = 0.048$). None of the other medication variables was significant (all ps > 0.10).

One of the largest studies to examine cognition in schizophrenia included 3365 patients from the SUPER-Finland cohort who met inclusion criteria and completed the Cambridge Neuropsychological Test Automated Battery; among them, 845 (25%) were current BZD users.[20] After adjusting for medications, anticholinergic burden, and other demographic variables, BZD use (versus nonuse) slowed mean reaction time by 20 ms ($B = 20.08 \pm 5.00$, $\beta = 0.07$, $p < 0.001$) and movement time by 17 ms ($B = 17.28 \pm 6.29$, $\beta = 0.05$, $p = 0.006$). BZDs also increased learning errors by about 1.5 errors in the paired-associates learning test ($B = 1.52 \pm 0.77$, $\beta = 0.03$, $p = 0.048$). Conversely, SNRI use (versus nonuse) was associated with faster reaction time, movement time, and fewer errors.

Benzodiazepines for Schizophrenia Symptoms

The first Cochrane review on this topic analyzed 34 studies involving 2657 patients, examining BZDs for different aspects of treatment, including rapid tranquilization.[21] Eight trials compared BZDs to placebo, 14 evaluated BZD monotherapy versus antipsychotic monotherapy, and 20 compared BZD augmentation of antipsychotics with antipsychotic monotherapy. These studies, published between 1962 and 2007, varied in length from 1 to 10 weeks and included 12 to 301 participants. Commonly used BZDs were diazepam, chlordiazepoxide, clonazepam, and lorazepam with haloperidol being the most frequent antipsychotic. Most studies were inpatient-based. When compared with placebo, BZD monotherapy showed no significant difference in clinical response rates (risk ratio [RR] 0.67, 95% CI 0.44-1.02), and its effects on global and mental state were inconsistent. Compared with antipsychotic monotherapy, BZD monotherapy showed no statistical difference in clinically

important treatment response at various time points (30 minutes, 60 minutes, 12 hours; RRs ranging from 0.61 to 1.48) though they induced sedation more quickly at 20 and 40 minutes. In combination with antipsychotics, BZDs provided a statistically significant short-term benefit in the first 30 minutes (RR 0.38, 95% CI 0.18-0.80) but showed no long-term improvements in global or mental state. Overall, there is no strong evidence supporting the routine use of BZDs as monotherapy or adjunctive therapy in schizophrenia though they may provide short-term sedation. High-quality, long-term studies are needed to better define their role in treatment.

A subsequent review by the same authors focused on adjunctive BZDs for psychotic symptoms, excluding ultra short-term studies (trial duration <1 week).[22] Six RCTs with 511 total participants were evaluable for achievement of the primary outcome, defined as a 50% reduction of the baseline PANSS or BPRS scores (when those criteria were not provided, the authors deferred to how it was defined in the original studies). The authors found that BZD augmentation was not associated with improved treatment response (RR 0.97, 95% CI 0.77-1.22), concluding that BZDs should not be used for schizophrenia outside of short-term sedation for acute agitation.

The most recent Cochrane review analyzed 20 trials with 695 participants evaluating BZDs for psychosis-induced agitation or aggression, either alone or combined with other medications, compared with placebo, antipsychotics, or antihistamines.[23] The overall quality of evidence was low or very low due to small sample sizes and significant risk of bias with no strong support for BZD use in managing agitation. When comparing BZDs to placebo, 1 trial ($n = 102$) found no difference in sedation at 24 hours (very low-quality evidence), but more participants receiving placebo showed no improvement in agitation in the medium term (1 to 48 hours) (RR 0.62, 95% CI 0.40-0.97). In BZDs versus antipsychotics, 8 trials ($n = 434$) found no significant difference in sedation at 16 hours (RR 1.13, 95% CI 0.83-1.54, low-quality evidence), and 5 trials ($n = 188$) found no difference in medium-term improvement (RR 0.89, 95% CI 0.71-1.11). A small study ($n = 150$) found that fewer patients improved with BZDs compared with olanzapine (RR 1.84, 95% CI 1.06-3.18, very low-quality evidence), whereas BZDs were associated with fewer extrapyramidal effects than haloperidol (6 trials, $n = 233$, RR 0.13, 95% CI 0.04-0.41, low-quality evidence). When comparing BZDs to antipsychotic/antihistamine combinations, 1 trial ($n = 200$) found a higher risk of no improvement in agitation with BZDs (RR 2.17, 95% CI 1.16-4.05, low-quality evidence). Sedation effects varied depending on the BZD used; lorazepam had a lower risk of sedation than the combination (RR 0.91, 95% CI 0.84-0.98), whereas midazolam had a higher risk of sedation (RR 1.13, 95% CI 1.04-1.23). Finally, for other combinations, data comparing BZDs plus antipsychotics to BZDs alone showed no significant differences (very low-quality evidence). When comparing BZDs plus antipsychotics with antipsychotics alone (haloperidol), 4 trials ($n = 185$) found no difference in improvement (RR 1.17, 95% CI 0.93-1.46) though sedation was more likely with the combination (3 trials, $n = 172$, RR 1.75, 95% CI 1.14-2.67, very low-quality evidence). One small study ($n = 60$) comparing BZDs plus antipsychotics with antihistamine/antipsychotic combinations found a higher risk of no improvement in agitation (RR 25.00, 95% CI 1.55-403.99) and increased sedation (RR 12.00, 95% CI 1.66-86.59, very low-quality evidence).

Akathisia

A systematic review and network meta-analysis evaluating the comparative efficacy and acceptability of various treatments for antipsychotic-induced akathisia identified 2 trials investigating BZDs, specifically clonazepam. The analysis suggested that clonazepam may be beneficial ($k = 2$, $n = 13$; standardized mean difference −1.62, 95% CI −2.64 to −0.59); however, the quality of evidence was low.[24] In the first trial, only about half of the patients had a diagnosis of schizophrenia or schizoaffective disorder,[25] whereas in the second trial, all participants had one of these diagnoses.[26] Another investigation found that long-term BZD use did not lower the risk of chronic akathisia, suggesting they may not be effective for long-term prevention.[27] Antipsychotic polypharmacy was associated with a higher risk of akathisia, and BZDs did not mitigate this risk, underscoring the need for cautious use and regular reevaluation of BZD prescriptions in managing akathisia.

Tardive Dyskinesia

A Cochrane review assessed the efficacy of BZDs in treating antipsychotic-induced tardive dyskinesia (TD).[28] There were 4 trials with a total of 75 participants, the majority of whom were men in their 50s with various psychiatric disorders. However, most participants had a primary diagnosis of schizophrenia. BZDs showed no clinically significant improvement (>50% improvement on any TD scale) in TD symptoms compared with placebo or no treatment after 5 to 10 weeks (very low-quality evidence; 2 randomized controlled trials [RCTs], 32 participants; RR 1.12, 95% CI 0.60-2.09, $I^2 = 14\%$). Similarly, there was no difference in the likelihood of showing no improvement in TD symptoms between BZDs and placebo or no treatment (2 trials, 32 participants; RR 1.49, 95% CI 0.33-6.74, $I^2 = 0\%$). The risk of symptom deterioration was also comparable between BZDs and placebo or no treatment (very low-quality evidence; 2 trials, 30 participants; RR 1.48, 95% CI 0.22-9.82, $I^2 = 19\%$). Findings on mean TD score changes were inconsistent with 1 trial showing no difference between diazepam and placebo (1 RCT, 17 participants; mean difference [MD] −0.29, 95% CI −1.57 to 0.99), another favoring treatment as usual over diazepam (1 RCT, 13 participants; MD 5.80, 95% CI 0.49-11.11), and a third demonstrating a benefit of clonazepam over placebo (1 RCT, 24 participants; MD -3.22, 95% CI −4.63 to −1.81).

Catatonia

There is a paucity of data from controlled trials on BZD use in catatonia as a Cochrane review only identified 1 evaluable trial.[29] This comparison of lorazepam and oxazepam for catatonia found no clear difference between treatment groups in terms of clinically significant symptom improvement defined as at least a 50% reduction on the Visual Analog Scale (VAS) (RR 0.95, 95% CI 0.42-2.16; 1 study, 17 participants; very low-quality evidence). Similarly, there was no significant difference between the 2 treatments in overall symptom change based on the average total VAS score at the study endpoint (MD 1.18, 95% CI −1.99 to 4.35; 1 study, 17 participants). No data comparing BZDs with placebo were available.

Discussion

Publications on BZD use in schizophrenia became more concerning around 2010 when the association between BZD use and mortality was first reported.[3] In total, there have been 5 separate studies showing increased mortality.[3-7] The studies consistently demonstrate that BZD use in schizophrenia is associated with increased mortality; the risk is greatest with long half-life agents, higher doses, and when they are used without antipsychotics. The increased risk spans both suicide and other causes of death.

Additionally, hospitalized patients with schizophrenia receiving BZDs face a markedly elevated HAP risk. Whereas BZDs as a class may increase risk by 3 times that of a nonuser,[8] specific agents such as midazolam may have an even higher risk (ie, more than sixfold).[9]

Two studies highlighted the negative impact of BZD use on rehospitalization rates in patients with schizophrenia.[10,11] BZD use was associated with a nearly doubled risk of readmission for OADA, whereas the other study linked high-dose BZD prescriptions to faster rehospitalization. These findings further suggest that BZDs may exacerbate psychiatric symptoms and increase hospital readmission risks in schizophrenia.

Other studies highlighted the complex impact of BZD use on brain volume, cognition, and quality of life in schizophrenia.[12-20] Whereas some studies show a correlation between high BZD doses and brain structure changes, others suggest cognitive improvements when BZDs are tapered. However, long-term BZD use is consistently linked to impaired cognitive functioning, particularly in attention and memory, and poorer quality of life outcomes.

Regarding schizophrenia symptom management, there have been 3 major Cochrane reviews,[21-23] none of which have found that there is solid evidence to support or refute the effectiveness of BZDs in any phase of the illness, including short-term agitation and aggression according to the most recent review of data specific to short-term use.[23]

That being said, BZDs are used to manage side effects and other associated conditions in those with schizophrenia, such as akathisia, tardive dyskinesia, and catatonia.[24-29] Although clonazepam showed promise for acute akathisia in 2 small trials, the very low quality and limited sample size mean its benefits must be interpreted with caution. Moreover, long-term BZD use did not prevent chronic akathisia, nor did it counteract the elevated risk associated with antipsychotic polypharmacy. Whereas the American Academy of Neurology 2013 guideline on the management of tardive syndromes[30] and the 2018 update from the same group[31] endorses clonazepam with a level B recommendation (1 class I study), the Cochrane review[28] excluded the trial on which the recommendation was based, citing that extraction of the study's data was not possible being that it was only presented in a graphic and the raw data was not available from the original authors. However, whereas there was only 1 trial identified by a Cochrane review,[29] consensus guidelines from the British Association for Psychopharmacology outline clear recommendations for either BZDs or electroconvulsive therapy in the treatment of catatonia.[32]

As shown in the Table, numerous schizophrenia guidelines have statements on the use of BZDs.[33-38] However, in many of the guidelines, the risk seems to be understated. For example, the American Psychiatric Association (APA) schizophrenia guidelines state, "... long-term use of benzodiazepines may be associated with increased risk of poorer outcomes, including side effects or misuse."[36(p40)] This statement from the APA in their guideline may lack the appropriate detail to call out the serious risk of these medications.

Conclusion

The findings from this scoping review underscore the critical need for more clear and universal guidelines on the use of BZDs in the treatment of schizophrenia. Whereas BZDs may be used for short-term management of acute symptoms or side effects, their long-term use poses significant risks.

To optimize treatment outcomes and ensure patient safety, it is imperative to develop comprehensive, evidence-based guidelines that address the appropriate use of BZDs in schizophrenia. Further research is needed to better understand the benefits and risks of BZDs in this patient population and to develop targeted interventions that improve overall treatment efficacy and safety.

TABLE: Comment on benzodiazepines

Schizophrenia Guideline	Comment on Benzodiazepines
RANZCP 2016[33]	BZDs can be used to initially treat distress, insomnia, and agitation BZDs may be used with parenteral administration of antipsychotics when a patient refuses oral medications and urgent control of agitation is required BZDs can be used when cross-titrating between antipsychotics if rebound psychosis or EPS presents BZDs do not have good evidence for long-term use but can be used for managing anxiety or brief symptom exacerbations BZDs (eg, lorazepam) can be given with antipsychotics for the management of acute behavioral disturbances when nonpharmacologic options have failed
Canadian 2017[34]	BZDs have been studied for managing aggression and hostility, but they are not recommended. Instead, clozapine is the preferred treatment
British Association for Psychopharmacology 2020[35]	BZDs may be appropriate for short-term treatment of anxiety or insomnia
American Psychiatric Association 2020[36]	BZDs are an option for akathisia, catatonia, NMS, and TD Research on their use in schizophrenia is limited, and long-term use may lead to poorer outcomes such as side effects or misuse
Psychopharmacology Algorithm Project (2013 Published Journal Version; 2020 Algorithm)[37]	BZDs are an option for akathisia BZD use in schizophrenia is linked to increased suicide-related mortality and a higher overall risk of death, so their use is not recommended in cases of suicidality or active substance use
European Psychiatric Association guidance on treatment of cognitive impairment in schizophrenia 2022[38]	BZD use should be limited due to detrimental effects on cognition

BZD = benzodiazepines; EPS = extrapyramidal symptoms; NMS = neuroleptic malignant syndrome; RANCZP = Royal Australian and New Zealand College of Psychiatrists; TD = tardive dyskinesia.

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