# Prevalence, risk factors, screening and approach of non-medical use of z-drugs and benzodiazepines in children, adolescents and young adults: a systematic review

Elien Acke, Lore Geypen, Caroline Van de Pol & Sarah Vandenabeele (KU Leuven)

Promotor: Prof. Dr. C. Matheï, Prof. Dr. M. Van Nuland (KU Leuven)

Co-promotoren: Kristien Coteur (KU Leuven)

Master of Family Medicine

Masterproef Huisartsgeneeskunde

Academiejaar: [2019– 2022]

*Deze masterproef is een examendocument dat niet werd gecorrigeerd voor eventueel vastgestelde fouten. Zonder voorafgaande schriftelijke toestemming van zowel de promotor(en) als de auteur(s) is overnemen, kopiëren, gebruiken of realiseren van deze uitgave of gedeelten ervan verboden. Voor aanvragen tot of informatie i.v.m. het overnemen en/of gebruik en/of realisatie van gedeelten uit deze publicatie, wendt u tot de universiteit waaraan de auteur is ingeschreven.*

*Voorafgaande schriftelijke toestemming van de promotor(en) is eveneens vereist voor het aanwenden van de in dit afstudeerwerk beschreven (originele) methoden, producten, schakelingen en programma's voor industrieel of commercieel nut en voor de inzending van deze publicatie ter deelname aan wetenschappelijke prijzen of wedstrijden.*

# Table of contents

**Acknowledgements** **5**

**Abstract** **6**

**Korte samenvatting** **7**

**Abbreviations** **8**

**Introduction** **9**

**Methods** **10**

*Selection criteria* *10*
Study design 10
Sample size, study subjects and characteristics 10
Language and time restrictions 10
Setting and geographic restriction 10

*Search strategy* *11*
Information sources 11
Search terms 11
Selection process and quality appraisal 11

*Data extraction* *11*
Data items 11
Synthesis of the results 12

**Results** **12**

*Search strategy* *12*

*Quality assessment* *13*

*Prevalence* *14*
Age 14
Students 15
High school students 15
College/university students 16
Medical students 18
Gender 19

*Correlations, associations and risk factors* *20*
Mental health 20
Medical use and BZD prescription 20
Perceptions 21
Co-ingestion 21
Race/ethnicity 21
Environmental factors 21
Geographic area 22
Sexual identity 22
Public vs. private schools 22
Educational status 23
Socioeconomic status / insurance 23
Criminality 23

*Screening methods* *23*

*Approaches* *24*

**Discussion** **24**

*Key findings* *24*

*Strengths and limitations* *25*

*Hypotheses and future research* *26*

**Conclusion** **27**

**Persoonlijke reflectie** **28**

**References** **30**

**Appendix A** **37**

**Appendix B** **44**

## Acknowledgements

We would like to express our gratitude to our promoters Prof. Dr. Matheï and Prof. Dr. Van Nuland for providing us with valuable guidance during the writing of this thesis. We also would like to thank our co-promoter Kristien Coteur for her helpful advice and support during this project. Furthermore, we wish to acknowledge the help provided by Shani De Coster and Lore Raets during the screening process.

# Abstract

*Background*: Benzodiazepines and z-drugs ((z-)BZDs) are widely prescribed drugs for different mental health disorders. Not only an increase in their prescription rate is noted, but also the rate of non-medical use (NMU) of these drugs rises. Because adolescents and young adults are vulnerable for the development of mental health disorders, it is important for health care practitioners to be aware of the risks associated with (z-)BZD use in these age categories.

*Methods*: We performed a systematic review investigating prevalence, risk factors, screening tools and approaches for NMU of (z-)BZDs in children, adolescents and young adults from 6 to 25 years. Different databases were screened and eventually 108 full text articles were analyzed while performing a quality assessment.

*Results*: Subjects aged 12 to 18 years showed lower rates of ever having misused (i.e. lifetime misuse) (z-)BZDs in comparison to people aged 18 to 25 years (1.4% to 3% versus 19%). There was a lack of research focusing on children from the age of 6 to 12 years. Lifetime prevalence rates of NMU of (z-)BZDs in high school and college students varied from 0.43% to 21% and 1.1% to 12.2% respectively. Generally, females were more likely to engage in (z-)BZD misuse than males. Current or past year mental health problems, a history of having received a prescription for (z-)BZDs, reporting (z-)BZD misuse by peers and Caucasian race were associated with an increased risk of NMU of (z-)BZDs. Data regarding other risk factors was scarce and not consistent. A large part of (z-)BZD misusers (26.3% to 72.6%) engaged in co-ingestion of other legal or illegal substances. There was no data concerning screening and approach of (z-)BZD misuse specifically.

*Conclusion*: (Z-)BZDs are frequently misused prescription drugs among adolescents and young adults. They are often used in combination with other substances (e.g. alcohol, club drugs), which increases health risks. Risk factors that predispose for (z-)BZD misuse are mental health problems, current and past medical use of (z-)BZDs, (z-)BZD misuse by peers and Caucasian race. To develop screening tools and intervention strategies for this population at risk, future research should focus more on both risk and protective factors.

# Korte samenvatting

*Achtergrond*: Benzodiazepines en z-drugs ((z-)BZDs) zijn geneesmiddelen die frequent worden voorgeschreven voor verschillende psychische aandoeningen. Naast een toename in het voorschrijven van (z-)BZDs, stelt men ook een toename in het misbruik hiervan vast. Adolescenten en jongvolwassenen zijn kwetsbaar voor de ontwikkeling van psychische aandoeningen. Daarom is het belangrijk dat zorgverleners zich bewust zijn van de risico's die gepaard gaan met het gebruik van (z-)BZDs in deze leeftijdscategorie.

*Methoden*: We voerden een systematische review uit om de prevalentie, risicofactoren, screeningsmethoden en aanpak van (z-)BZDs misbruik door kinderen, adolescenten en jongvolwassenen tussen 6 en 25 jaar te onderzoeken. Verschillende databanken werden onderzocht. Uiteindelijk werden 108 artikels geanalyseerd en beoordeeld op kwaliteit.

*Resultaten*: 12- tot 18-jarigen misbruiken minder frequent (z-)BZDs dan 18- tot 25-jarigen (1.4% tot 3% versus 19% lifetime prevalentie). Er waren geen artikelen beschikbaar betreffende 6- tot 12-jarigen. Bij studenten in het middelbaar en het hoger onderwijs varieerde de lifetime prevalentie respectievelijk van 0.43% tot 21% en van 1.1% tot 12.2%. Over het algemeen was er meer misbruik van (z-)BZDs bij vrouwen dan bij mannen. Volgende factoren waren geassocieerd met een verhoogd risico op (z-)BZD misbruik: de aanwezigheid of voorgeschiedenis van psychische gezondheidsproblemen, voorgeschreven (z-)BZDs in het verleden, kaukasisch ras en misbruik van (z-)BZDs door familie en vrienden. Gegevens over andere risicofactoren waren zeldzaam en inconsistent. Een groot deel van de personen met misbruik van (z-)BZDs (26.3% tot 72.6%) nam gelijktijdig andere legale of illegale middelen in. Er was geen informatie beschikbaar over screening en aanpak van misbruik specifiek voor (z-)BZDs.

*Conclusie*: (Z-)BZDs zijn geneesmiddelen op voorschrift die frequent misbruikt worden door adolescenten en jongvolwassenen. Ze worden vaak gelijktijdig gebruikt met andere middelen (bijvoorbeeld alcohol, club-drugs), hetgeen verhoogde gezondheidsrisico's met zich meebrengt. Risicofactoren die voorbeschikken voor het misbruik van (z-)BZDs in adolescenten en jongvolwassenen zijn psychische gezondheidsproblemen, het gebruik van (z-)BZDs in het verleden, misbruik ervan door familie of vrienden en het kaukasisch ras. Toekomstig onderzoek zou verder moeten focussen op risicofactoren en beschermende factoren. Dit met het oog op de ontwikkeling van screeningsmethoden en interventiestrategieën voor adolescenten en jongvolwassenen die een verhoogd risico hebben op het misbruiken van (z-)BZDs of deze reeds misbruiken.

## Abbreviations

| | |
|---|---|
| AD | Anxiety disorder |
| ADHD | Attention-deficit/hyperactivity disorder |
| AOR | Adjusted odds ratio |
| ASD | Autism spectrum disorder |
| BZD | Benzodiazepine |
| CI | Confidence interval |
| CM | Contingency management |
| CRAFFT | Car, Relax, Alone, Forget, Friends, Trouble |
| FPIA | Fluorescence Polarization Immunoassay |
| GHQ12 | General Health Questionnaire |
| LDQ | Leeds Dependence Questionnaire |
| MUPD | Medical use of prescription drugs |
| NHLBI | National Heart, Lung and Blood Institute |
| NMU | Non-medical use |
| NMUPD | Non-medical use of prescription drugs |
| NSDUH | National Survey on Drug Use and Health |
| OR | Odds ratio |
| PD | Psychological distress |
| SAD | Separation anxiety disorder |
| US | United States |
| (Z-)BZDs | Z-drugs and benzodiazepines |

# Introduction

Z-drugs and benzodiazepines ((z-)BZDs) are commonly and widely prescribed drugs for different indications like depression, insomnia and anxiety disorders (ADs) (1,2). A significant amount of the first prescriptions of these drugs originated from primary health care. For example, Sidorchuk et al. (2018) found that 40.7% of the study participants between the age of 0 and 24 got their prescription from primary care (3). Besides the common use of these drugs by adults, an increase in their prescription rate and (long-term) use is noted in the younger population, even though the reason for their prescription is not always justified (3,4).

There are few medical indications that legitimize (z-)BZD use. As a matter of fact, in children and adolescents, epilepsy and seizures are currently the only approved indications for (z-)BZD usage (3,5,6). However, (z-)BZDs are also commonly used for the treatment of sleep and ADs in this population (3). It is widely acclaimed that adolescence is a crucial stage of life in which young adults face several challenges, including achievement of independence and formation of identity. Due to these challenges, adolescence and young adulthood are periods in which many mental disorders emerge (7,8). In these circumstances sleep disorders are prevalent, especially in patients with neurodevelopmental disorders, like attention-deficit/hyperactivity disorder (ADHD) or autism spectrum disorder (ASD). Sleep disorders can consequently have a major impact on daily functioning, behavior and overall quality of life (9). (Z-)BZDs are sometimes used to address the problem of insomnia in adolescence and young adulthood, although not always indicated (3).

One should always be aware of the possible risk of dependency and non-medical use (NMU) of these prescription drugs. For example, self-regulation of negative emotions and the need for dissociation from their environment pushes young adults to use (z-)BZDs in a non-medical way (10,11).

In addition, there are some other important side effects of (z-)BZDs that must be taken into account, such as a negative impact on cognitive functions (12,13). Long-term use of BZDs could lead to an impairment in long-term memory. These adverse effects are already frequently established in the adult population, but there is a need for information about the impact of long-term (z-)BZD use in the younger age group (12).

To identify patients with an increased risk of (z-)BZD misuse, more information is needed about risk factors and screening tools (14). Based on previous studies, BZD misuse seems to be correlated with different factors like excessive alcohol use, concurrent dispensation of other psychotropic drugs and many more (15). Further knowledge of these characteristics is important for primary health care practitioners to ensure better guidance of a patient (mis)using (z-)BZDs. Although the prescription rate and thereby the misuse of (z-)BZDs significantly increases, guidelines regarding prescription and use of these drugs are scarce. The lack of guidelines makes safe and responsible prescription of (z-)BZD challenging (16,17).

Previous studies established a significant difference in prevalence of (z-)BZD use between children, adolescents and adults. This difference is possibly due to different indications for prescription and safety concerns within the younger age group. Moreover, the discrepancy between the different age groups could also be caused by a lack of studies and failure of the replication of studies within this young study population (3,17).

The objective of this review is to assemble the current available literature on the misuse of (z-)BZDs by children, adolescents and young adults. We will outline the prevalence of misuse in this population and define potential risk factors for misuse. Furthermore, we will compare screening methods for NMU of these drugs and different approaches to deal with (z-)BZD misuse.

# Methods

## Selection criteria

### Study design

The initial aim was to perform a scoping review with no limitation for inclusion based on study design. However, because of the large amount of included studies after screening, this study was narrowed to a systematic review. Eventually, observational and intervention studies with a longitudinal or a cross-sectional research design were included. Both prospective and retrospective studies were included, as well as studies with an experimental design and case-control studies. Qualitative studies, opinion articles, book reviews, commentaries, case reports and editorial reviews were excluded.

### Sample size, study subjects and characteristics

There was no limitation on the sample size for the inclusion of studies. Studies investigating children, adolescents and young adults from the age of 6 to 25 were included. According to the definition used in development psychology, patients were subdivided in three categories: children in school period (age 6 to 12), adolescents (age 12 to 21) and young adults (age 21 to 25) (18,19). Studies wherein both the upper and lower limit of the 95% confidence interval (CI) lies within this age range were included. Studies investigating high school and university students without further specification of the age range were also included.
We covered NMU of (z-)BZDs and abuse of non-medically used (z-)BZDs (e.g. flunitrazepam). NMU involves using a drug that was not prescribed, using a drug otherwise than prescribed on purpose or using a drug for other reasons than prescribed (e.g. for self-regulation or recreational use).

### Language and time restrictions

Studies available in English, Dutch or French were included. The search was not limited by a time restriction.

### Setting and geographic restriction

Studies were not excluded based on their setting. The search was not restricted to a geographical region.

## Search strategy

### Information sources

Literature was collected from databases Pubmed, Embase, Web of Science, CINAHL, PsycArticles and Cochrane library. The literature search was performed on the 23th of September 2020.

### Search terms

The search was conducted with different combinations of terms depending on the databases. The search strategy was built upon three concepts. Concepts were first constructed using mesh terms in Pubmed and were subsequently converted to a suitable search strategy for other databases.

The first concept contained the type of drugs studied and was constructed using the terms benzodiazepines and z-drugs. The second concept indicated the age category of the investigated population and consisted of the terms adolescents, child, minors, pediatrics, puberty, students, schools, university, young adults and child psychiatry. The third concept contained NMU and was built starting from the terms drug misuse, addictive behavior, addiction medicine, substance-related disorders, substance abuse, poisoning and drug overdose.

An extended overview of the search strategies is represented in Appendix A.

### Selection process and quality appraisal

The obtained references were gathered in the screening tool “Rayyan QCRI" for screening purposes. After deduplication, articles were screened by two independent reviewers based on title and abstract. Next, the full text of the included articles was screened independently and a quality appraisal was performed using the Quality Assessment Tools of the National Heart, Lung and Blood Institute (NHLBI) (20). Any conflicts were resolved by discussion between reviewers. In case of uncertainties, the third and fourth reviewer were consulted, and if necessary also the supervisor and co-supervisor of this thesis project. The PRISMA 2020 checklist was used to improve transparency (21). Additionally, a PRISMA flow chart was made to depict the flow of information through the different phases of this review (21).

## Data extraction

### Data items

Standard bibliographical information (i.e. author, title, journal, study design and year of publication) was charted, as were study characteristics such as sample size, age groups, geographical location and setting. Also the type of misused drugs, prevalence and risk factors for NMU, reasons for misuse and age of first misuse were extracted. Furthermore, the scope and conclusion of the studies were charted. The obtained data were summarized in an overview in Excel. For every article, this analysis was conducted by one reviewer and verified by a second reviewer. In case of uncertainties, the other reviewers were consulted, and if necessary the supervisor and co-supervisor.

### Synthesis of the results

The collected data were represented in a narrative way accompanied by tables and figures when possible.

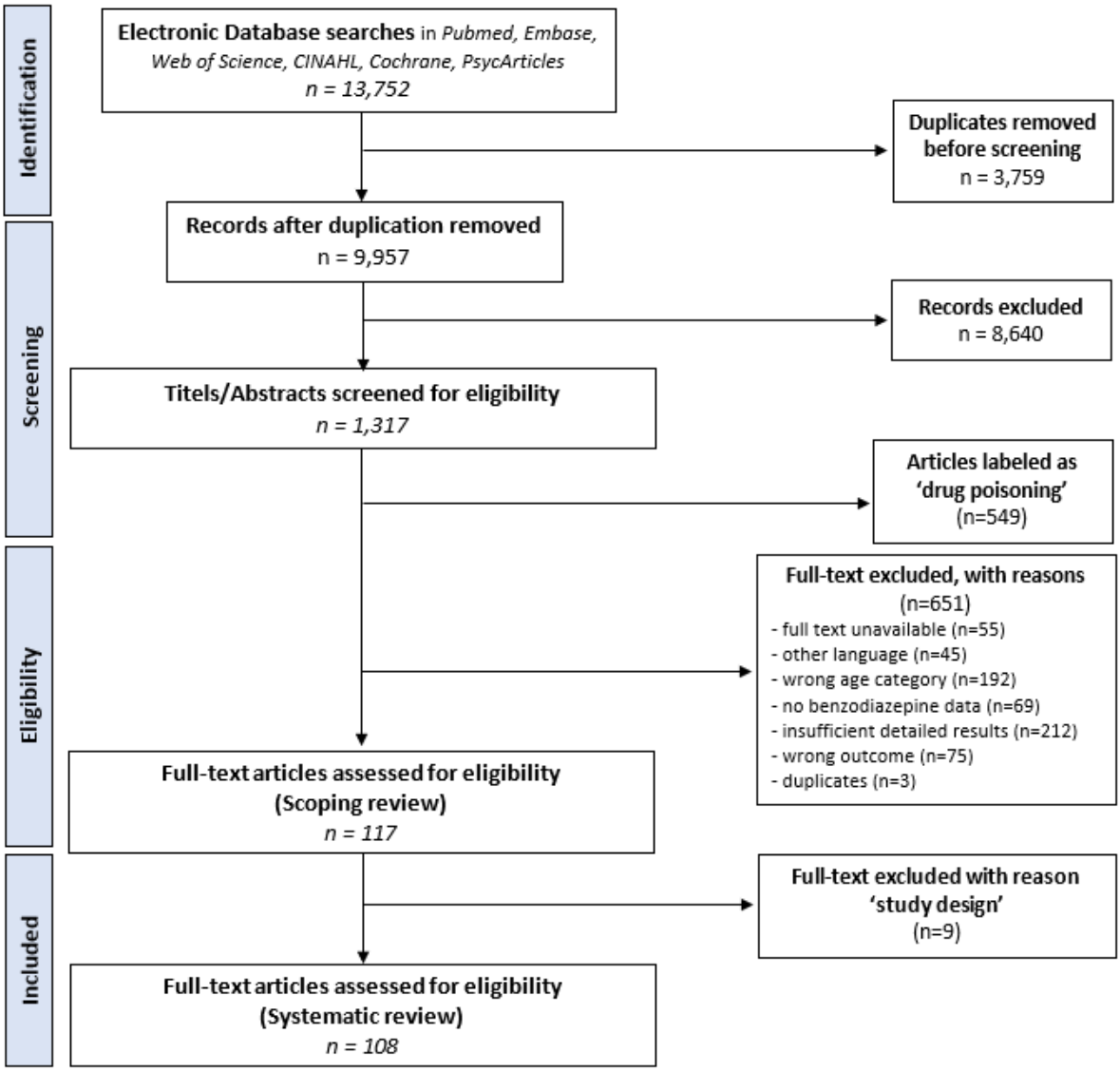
## Results

### Search strategy

The initial search strategy yielded 13,752 articles on the 23th of September 2020. Among them, 2,728 articles were derived from Pubmed, 7,804 from Embase, 1,425 from Web of Science, 1.052 from CINAHL, 282 from PsycArticles and 461 from Cochrane. 3,759 articles were removed as duplicates. The remaining 9,957 articles were imported in the systematic review tool "Rayyan QCRI". After screening on title and abstract, 1,316 articles remained for full-text review. Studies investigating drug poisoning (N=547) were labeled as such and screened by a separate research team. Subsequently, full-text analysis identified 118 articles in the non-poisoning section that met the inclusion criteria for our scoping review. Because the literature search was more extensive than expected, articles labeled as poisoning were excluded from this project since data processing of all articles was not feasible. When converting the study from a scoping review to a systematic review, nine more articles were excluded based on study design (e.g. abstract, case report, review). Eventually, 108 articles were included for full text analysis (Figure 1). Because of heterogeneous data, a meta-analysis was not performed.

**Figure 1**

*Study Selection Flowchart*

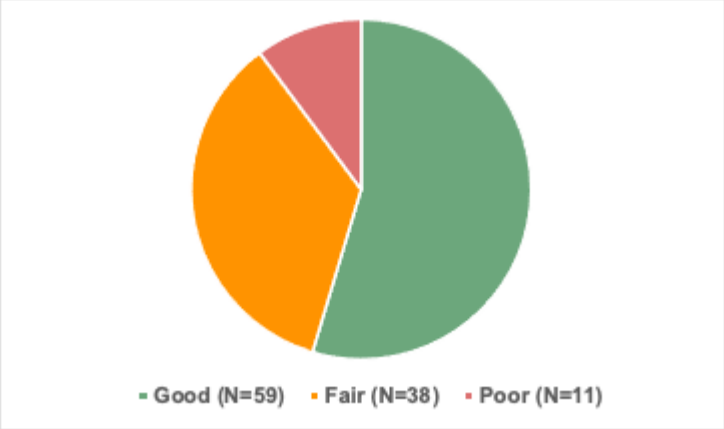



## Quality assessment

Overall, most studies were evaluated as having good quality (Figure 2). As shown in Figure 2, the quality was considered to be 'good', 'fair' or 'poor' for 59, 38 and 11 articles respectively. The main barriers for a good evaluation were related to sample size and outcome measures (questions 5, 6 and 10). A more detailed overview of the quality assessment outcomes can be found in Appendix B.

**Figure 2**

*Diagram of the Quality Assessment: 59 articles had good quality, 11 articles poor quality.*




## Prevalence

### Age

A limited number of studies included children under the age of 12 years old (22–27). One study reported a lifetime prevalence of non-prescribed use of tranquilizers (e.g. diazepam, lorazepam, flunitrazepam) of 2.2% (95% CI 1.8–2.6) in students aged 10 to 12 years (27). No further data about prevalence in this age category were found.

Prevalence of (z-)BZD misuse among people aged 12 to 18 years was regularly discussed. Lifetime prevalence rate of BZD misuse was reported 3% by Rigg et al. (including Klonopin, Xanax, Valium, Ativan and Librium) and 2.3% (95% CI 2.1–2.5; p≤0.00333) by Schepis 2018B et al. (including Xanax, Valium, Ambien and Lunesta) (27–29). Past year NMU of (z-)BZDs, tranquilizers (e.g. Valium, Librum, Xanax) and sedatives (e.g. Sonesta, Ambien, barbiturates) showed prevalence rates of 1.9% (95% CI 1.7-2.1; p≤0.00333), 2.2% (N=79 of a total of 3.614 adolescents) and 1.9% (N=67 of a total of 2.614 adolescents) (29,30).

Furthermore, Rigg et al. (2014) concluded that there was a significantly increased risk for misuse within older adolescents in this group (odds ratio (OR) 1.67) according to the bivariate and risk factor model. Boyd et al. (2015) supported this finding with an increment of the odds of NMU of anxiolytic or sleep medication in association with an older age (AOR 1.21; 95% CI 1.09–1.36; p≤0.001) (31).

The lifetime and past year NMU of (z-)BZDs in people aged 18 to 25 years was higher in comparison to the younger age group (12 to 17 years). It was respectively 7.8% (95% CI 7.4–8.3; p≤0.00333) versus 2.3% (95% CI 2.1–2.5; p≤0.00333) for lifetime misuse and 5.8% (95% CI 5.4–6.2; p≤0.00333) versus 1.9% (95% CI 1.7–2.1; p≤0.00333) for past year misuse (29). There was no significant association between the different ages in this group and the past month misuse after stratification (p=0.363) (32). Alprazolam was the most commonly misused BZD within this age category with a prevalence from 87% to 96.5% (33,34). Another study found a similar prevalence of 88.3% although it was unclear which percentage comprised misuse (15).

## Students

### *High school students*

General non-medical use of prescription drugs (NMUPD) was prevalent in high school students, with lifetime prevalence rates varying from 6.5% (35) to 34% (36). Of these, BZDs were the second most misused prescription drugs (35–37).

The lifetime prevalence rate of NMU of BZDs in high school students varied between 0.43% (38) and 21% (39). Data of past year and past month misuse is shown in Table 1.

McCabe et al. (2014) found that 9.7% of high school seniors in the United States (US) showed a lifetime exposure to prescription BZDs (either medically or non-medically) (40). This study stated that NMU of BZD anxiolytics was more prevalent than medical use (7.5% versus (vs.) 4.9%).

In a population of high school students who were prescribed sleeping or anti-anxiety medication, a large number also have misused these prescribed medications in the past year, namely 43.9% for sleeping medication and 29.8% for anti-anxiety medication (41).

One study examined the lifetime and past month misuse of BZDs amongst 11th and 12th grade school students with a screening tool for substance use named 'Car, Relax, Alone, Forget, Friends, Trouble' (CRAFFT). Among students with scores ≥4, 50% had used BZDs at least once in their lifetime and 26% in the last 30 days. Prevalence data were summarized in Table 1. CRAFFT is further discussed in the section 'screening tools' (42).

**Table 1**

*An Overview of Prevalence Rates among High School Students*

| Author, year | Sample size (N) | Lifetime prevalence[a] of NMU of (z-)BZDs in total population | Past year NMU of (z-)BZDs | Past month NMU of (z-)BZDs | (z-)BZDs studied |
|---|---|---|---|---|---|
| Cakici, 2018 | 1487 | 2.1% | / | / | BZDs, not specified |
| Currie, 2012 | 44344 | 2.1% | / | / | sedatives or tranquilizers (such as Valium, Ativan and Xanax) |
| Falck, 2012 | 3974 | according to CRAFTT score: 4% (0-1), 18% (2-3), 50% (≥4) | / | according to CRAFTT score: 1% (0-1), 7% (2-3), 26% (≥4) | BZDs, not specified |
| Gana, 2019 | 3298 | 21% | / | / | Valium |
| Guimaraes, 2004 | 2123 | 3.8% | / | / | BZDs, not specified |
| Juan, 2015 | 84184 | 0.43% | 0.21% | 0.38% | diazepam |
| McCabe, 2007B | 1086 | 3.5% NMU in combination with medical use<br><br>2.4% NMU use | / | / | Sleeping medication (e.g., Ambien, Halcion, Restoril, temazepam, triazolam) |

| | | | | | |
|---|---|---|---|---|---|
| | | only | | | |
| | | 2.4% NMU in combination with medical use<br><br>1.2% NMU use only | / | / | Sedative/anxiety medication (e.g., Ativan, Xanax, valium, Klonopin, diazepam, lorazepam) |
| McCabe, 2012 | 12431 | / | 5.3% | / | Tranquilizers (e.g. Librium, Valium, Xanax) |
| McCabe, 2014 | 11248 | 7.5% | / | / | BZD anxiolytics (e.g. Ativan, Klonopin, Librium, Serax, Valium and Xanax) |
| Opaleye, 2013 | 18230 | 5.0% | 3.3% | = nearly half of those who used in the previous year (30% of lifetime users) | Tranquilizers/sedatives (e.g. diazepam, Dienpax, Valium, Lorax, Rohypnol, Psicosedin, Somalium, Apraz, Rivotril, alprazolam, Lexotan, Dalmadorm, Dormonid, bromazepam, Frontal, Olcadil |
| Sandi, 2002 | 304 | 2% | / | / | BZDs, not specified |
| Schepsis, 2016 | 11444 | / | 5.3% | / | Tranquilizers, not specified |

[a] Lifetime prevalence = the proportion of individuals that (up to the time of assessment) have misused (z-)BZDs at some point in their life

***College/university students***

General NMUPD is also quite prevalent in college students. Lifetime prevalence rates of NMUPD varied between articles from 20% (43) to 36.8% (44). (Z-)BZDs (often described as sedatives, anxiolytics or tranquilizers) accounted for 16.8% (45) to 39.8% (44) of all misused prescription drugs. Lifetime prevalence rates of NMU of (z-)BZDs in college students varied between 1.1% (46) and 12.2% (44). Further details regarding lifetime, past year and past month NMU of (z-)BZDs are shown in Table 2.

One article found that NMUPD (e.g. tranquilizers, stimulants, and pain relievers) was less frequent in first-year students, but did not describe data for BZDs specifically (44). Two articles also found a great difference across campuses in past year prevalence of NMU of BZDs, with rates varying from 0% to 20% (47,48). Also the type of misused BZD varied across degree programs (47).

**Table 2**

*An Overview of Prevalence Rates among College/University Students*

| Author, year | Sample size (N) | Lifetime prevalence[a] of NMU of (z-)BZDs in total population | Past year NMU of (z-)BZDs | Past month NMU of (z-)BZDs | (z-)BZDs studied |
|---|---|---|---|---|---|
| Benotsch, 2015 | 763 | 16.8% (Anxiolytics: 10.0%, sedatives: 6.8%) | / | / | Anxiolytics (e.g., Valium, Xanax), sedatives (e.g., Restoril, Ambien) |
| Brandt, 2014 | 303 | 12.2% | 30% of non-medical (z-)BZD users (= +/- 3.7% of total population) | 15% of non-medical (z-)BZD users (= ±1.8% of total population) | Xanax (alprazolam), Klonopin (clonazepam), Valium (diazepam), Ambien (zolpidem), and Ativan (lorazepam) |
| Gazibara, 2016 | 514 | 11.9% (7.6% bromazepam use and 4.3% diazepam use) | / | / | bromazepam, diazepam |
| Hagman, 2007 | 200 | 94% never use<br>3% <1x/month use<br>3% missing data | / | / | BZDs, not specified |
| Marin, 2010 | 4017 | 6.9% BZD use → 39% by self-medication | / | / | alprazolam, clonazepam, diazepam, bromazepam, lorazepam, flunitrazepam |
| McCabe, 2005 | 10904 | 7.8% | 4.5% | 1.6% | BZDs (e.g. Valium, Librium, Xanax, Ativan and Klonopin) |
| McCabe, 2008 | 3639 | 1.4% NMU in combination with medical use<br>3.0% NMU only | 0.7% NMU in combination with medical use<br>1.8% NMU only | / | Sleeping medication (eg, Ambien (zolpidem), Halcion (triazolam), Restoril (temazepam), temazepam, triazolam) |
| Olashore, 2018 | 401 | 1.1% | / | / | BZDs, not specified |

| | | | | | |
|---|---|---|---|---|---|
| Parks, 2020 | 1686 | / | 6.1% | / | Sedatives/anxiolytics (Xanax (alprazolam), Valium (diazepam), Ambien (zolpidem)) |
| Pino, 2017 | 2458 | 18.8% | / | 4.3% | Xanax, Valium, Klonopin, Ativan, or similar drug |
| Rezahosseini, 2014 | 1260 | 7.4% | / | / | BZDs, not specified |
| Stone, 2012 | 383 | 4.0% | / | / | BZDs, not specified |
| Zullig, 2011 | 22783 | / | 4.1% | / | Sedatives (e.g. Xanax or Valium) |

[a] Lifetime prevalence = the proportion of individuals that (up to the time of assessment) have misused (z-)BZDs at some point in their life

***Medical students***

The lifetime prevalence rates of NMU of BZDs in medical students varied between 0.9% (49) and 37% (50) (Table 3). According to the study of Paredes et al. (2008), the lifetime prevalence in nursing students was 10.5% (51). One study found that 7% of the pharmacy students used (z-)BZDs, of which 40.3% had a medical prescription, 23.8% did not use them for medical reasons, and 43.1% were self-medicating (52).

Only one study compared medical to non-medical students and found a significant higher use of Librium/calmpose in male medical students (12.74% for Librium, 5.31% for calmpose) compared to male non-medical students (1.97% for Librium, 0.49% for calmpose). In females, there was no significant difference (53).

**Table 3**

*An Overview of Prevalence Rates among Medical Students*

| Author, year | Sample (N) | Lifetime prevalence[a] of NMU of (z-)BZDs in total population | Past year NMU of (z-)BZDs | Past month NMU of (z-)BZDs | (z-)BZDs studied |
|---|---|---|---|---|---|
| Croen, 1997[b] | 170 (=1st year of medical school | 2.4% | / | / | BZDs, not specified |
| | 139 (=2nd year of medical school) | 5.8% | / | / | BZDs, not specified |
| Imran, 2012[b] | 1299 | 3.6% | / | / | BZDs, not specified |

| | | | | | |
|---|---|---|---|---|---|
| Khanal, 2010[b] | 466 | 1.3% | / | / | BZDs, not specified |
| Kushwaha, 2019 | 314 | 0.9% | / | / | Diazepam |
| Maddux, 1986 | 133 | 37% | 17% | 8.6% | BZDs, not specified |
| Nawaz, 2017[b] | 698 | 31% | / | / | BZDs, not specified |
| Paredes, 2008 | 181 | 10.5% | 6.1% | 3.9% (presently) | BZDs, not specified (list of most consumed BZDs given: clonazepam, lorazepam, alprazolam, bromazepam, ketazolam, others) |

[a] Lifetime prevalence = the proportion of individuals that (up to the time of assessment) have misused (z-)BZDs at some point in their life

[b] The term 'use' of BZDs was not specified, but it was described in a setting of misuse of other (illicit) substances

## Gender

The difference in (z-)BZD misuse among males and females varied a lot between articles. According to most of the articles young females were more likely to report the NMU of (z-)BZDs than males. In eleven studies this finding reached statistical significance (23,27–29,40,54–58).

In the age group from 12 to 18 years, Boyd et al. (2015) found that being female was associated with greater odds of NMU of (z-)BZD (AOR 1.82; 95% CI 1.06–3.11) for those with self-treating motives, such as decreasing anxiety or getting a better sleep (31). The results of Guimaraes et al. (2004) coincide with these findings. They found that the lifetime prevalence of BZD misuse in female Brazilian middle and high school students (4.9%) was significantly higher than males (2.8%) ($p<0.05$) (23). Likewise, Opaleye et al. (2013) found that female Brazilian students aged 13 to 19 years were twice as likely to report NMU of tranquilizers and sedatives during lifetime (AOR 2.19; 95% CI 1.75–2.75) (55). Opaleye et al. (2014) also found a two times higher prevalence of (z-)BZD use in girl students (10 to 18 years) compared to boys (AOR 2.00; 95% CI 1.76–2.26) (27). Likewise, males showed less BZD misuse than females in a large study sample with subjects aged 12 to 17 years (AOR 0.64; 95% CI 0.44–0.93) (28). Also, male secondary school students (2.4%) in the study of Currie et al. (2012) reported less misuse of sedatives and tranquilizers than females (1.9%) (AOR 0.80; 95% CI 0.79–0.81) (57).

Among people aged 18 years and older, Nigerian female students significantly had a higher lifetime consumption of diazepam ($p<0.05$) (56). Schepis et al. (2018) also found lower odds of past year BZD misuse in males (AOR 1.45; 95% CI 1.26–1.66) in the subjects aged 18 to 25 years (29). This finding is supported by Carrasco-Garrido et al. (2020) who found a significantly higher prevalence of non-prescription use of (z-)BZDs among young Spanish females from 19 to 34 years (males 1.13% (N=37) vs. females 2.02% (N=65), $p=0.00$) (54). Also Rezahosseini et al. (2014) concluded that BZD abusers aged 21.35 years (SD 2.73) were significantly more likely to be female ($p=0.002$) (58). Likewise, McCabe et al. (2014) found that the NMU of BZDs was significantly higher among female students (4.9%) than among their male counterparts (4.1%) ($p<0.01$) (40).

In other articles there was more (z-)BZD misuse among females than males, but these findings did not reach significance (14,51,59–65).

## Correlations, associations and risk factors

### Mental health

The link between current and past year mental health problems and the misuse of (z-)BZDs and other drugs was widely investigated. The most examined mental health problems are psychological distress (PD) and ADs. A history of past year mental health treatment was a recurring point of interest as well.

PD was established by questionnaires, more specifically by the National Survey on Drug Use and Health (NSDUH) survey and the 12-item General Health Questionnaire (GHQ12). The existence of PD symptoms was accompanied by greater odds of reporting BZD use with a range of 1.27 to 1.71 (64). Similarly, an increment of one-point in a PD scale caused a 9% increase in the odds of past year prescription BZD misuse in women (AOR 1.09; $p<0.001$; 95% CI 1.07–1.10) and a 7% increase in the odds in men (AOR 1.07; $p<0.001$; 95% CI 1.05–1.09) (66). Olashore et al. (2018) also confirmed a significant association between the current use of BZDs and PD. However, it was not clear whether they discussed misuse or prescribed use (46). Finally, the experience of mental distress induced an eightfold increase in odds of BZD dependence (34). Boyd et al. (2015) came to a similar conclusion, but they investigated the presence of depressive and anxiety symptoms specifically. Subjects with higher levels of these symptoms were more likely to enlist in NMU of sleeping and anxiety medication (AOR 1.02; 95% CI 1.02–1.10; $p\leq.01$) (31).

The history of a mental health treatment within the previous year significantly increased the odds of lifetime NMU of zolpidem with an OR of 2.87 (95% CI 2.23–3.70; $p<0.001$) for people aged 12 to 17 years and 2.96 (95% CI 2.46–3.56; $p<0.001$) for people aged 18 to 25 years. There was no significant age-based interaction with older subjects (14). Additionally, subjects with a past year mental health treatment showed significantly more NMU of tranquilizers (e.g. Xanax, Ativan) in comparison to those without past year mental health treatment (67).

However, a subsequent study found lower misuse odds for subjects aged 12 to 17 and 18 to 25 years that underwent past year mental health treatment. The OR for past year sedative/tranquilizer misuse in these age categories was 0.76 (95% CI 0.58–0.99; $p\leq0.05$) and 0.55 (95% CI 0.44–0.67; $p\leq0.001$) respectively (29).

Furthermore, the presence of a past year AD was also significantly associated with lifetime NMU of zolpidem with an OR of 6.54 (95% CI 4.56–9.37; $p<0.001$) for people aged 12 to 17 years and 3.18 (95% CI 2.48–4.07; $p<0.001$) for people aged 18 to 25 years. Likewise, past year NMU of these drugs was affected by the presence of past year AD for both people aged 12 to 17 years (OR 8.11; 95% CI 4.79–13.73) and people aged 18 to 25 years (OR 4.54; 95% CI 3.31–6.24) (14). Viana et al. (2012) confirmed that panic disorder and separation anxiety disorder (SAD) symptoms were significant predictors of NMUPD with an OR of 2.04 (95% CI 1.49–2.79; $p<0.001$) and 1.4 (95% CI 1.01–2.00; $p<0.001$) respectively (35).

### Medical use and BZD prescription

A history of medical use or having ever received a prescription for BZDs are both associated with NMU of these drugs. This is the case for current as well as past medical use of BZDs (29,31,43,55). More specifically, NMU of (z-)BZDs was six to nine times more frequent in adolescents that had received a recent prescription (31).

## Perceptions

A low-risk perception for NMU of (z-)BZDs is strongly associated with higher consumption of these drugs among young Spanish adults (AOR 3.88; 95% CI 2.53–5.93) (54). Furthermore, the results of Rickert et al. (1999) show misusers (women 14 to 26 years of age) of BZDs, more specifically flunitrazepam, had a lower perception of risk of experimental use (≤ 2 times) of these drug than non-users ($p<0.001$) (68). This is in contrast to the risk perception of regular use of flunitrazepam which was not significantly different to non-users (68).

In addition, adolescents with a negative perception of their own health were two times more likely to report misuse of (z-)BZDs compared to those who expressed a positive perception of their health (AOR 2.21; CI 1.30–3.76) (54).

However, Stone et al. (2012) concluded that students who had a more positive belief toward BZD-seeking also reported more BZD-seeking behavior (69).

## Co-ingestion

Non-medical (z-)BZD users were more likely to misuse other substances and illicit drugs compared to people who used these drugs medically. This association almost always reached statistical significance. For example, higher past month cigarette use, binge drinking and use of other (illicit) substances (e.g. cocaine, marijuana, ecstasy, LSD, heroin and prescription stimulants) were reported by (z-)BZD misusers (37,40,44,48,60,68,70–74). Moreover, NMU of prescription opioids was even 30 times more frequent in this population (OR 32.13, $p<0.001$) (48). Conversely, misusers of prescription opioids were at least 15 times more likely to engage in NMU of tranquilizers or sedatives (29). In adolescents aged 12 to 18 years, Ford et al. (2012) reported an increased risk of Ambien misuse in subjects engaging in binge drinking (AOR=5.25), tobacco use (AOR=4.47), marijuana use (AOR=7.28) and the use of other prescription drugs (AOR=14.17) (60). Overall, co-ingestion rates of NMU of BZDs with other substances or illicit drugs varied from 26.3% (44) to 72.6% (67).

## Race/ethnicity

All studies investigating correlations between race and (z-)BZD misuse found that BZD misuse was more likely to occur in white/Caucasian people compared to other races (14,31,35,37,48,60,63,66,68,69,71,75), although Schepis et al. (2018) only found this association in subjects aged 18 to 25 years and not in subjects aged 12 to 17 years (29).

One study found even eight times higher flunitrazepam using rates in whites compared to blacks ($p\leq0.05$). Hispanics in this study also showed ten times higher using prevalence rates than blacks ($p\leq0.05$) (71). The latter is contradicted by McCabe et al. (2005), who stated that NMU of prescription BZD anxiolytics was less likely to occur among college students who were Asian or Hispanic (48).

Black race was associated with lower odds of BZD dependence, although it failed to reach significance in the multivariate model (34,71).

### Environmental factors

NMU of (z-)BZDs was more frequent among people who know someone who had misused a BZD or who reported tranquilizer/sedative use by a friend or family member (55,60,68,69,72). In one study, 4% of the entire sample

even reported peer pressure for flunitrazepam use and this experience of pressure was three times higher in flunitrazepam users compared to non-users (68).

Another risk factor for BZD dependence is childhood abuse (OR 2.1), although this failed to reach significance in the multivariate model (34). When looking at risk factors for potential flunitrazepam use, Rickert et al. (2000) did not found higher intention of flunitrazepam use in subjects that had ever experienced physical or sexual victimization (76)

## Geographic area

One study found two times higher prevalence rates of BZD anxiolytics in students who attended college in the Southern region of the US compared to students attending college in the North Central region (48). This finding is supported by Sheridan et al. (2019) who found that the highest amount of intentional BZD abuse occurs in the South (Northeast 7.7%, South 11.5%, Midwest 8.5%, West 4.3%) (77).

Data of urban and rural differences in (z-)BZD misuse are contradicting. To be resided in a small ($p \leq 0.01$) as well as a large ($p \leq 0.05$) metropolitan area was associated with higher flunitrazepam use (71) and there were more referrals for BZD addiction treatment in urban areas compared to rural areas (78). Adelekan et al. (1989) also found higher diazepam use rates in urban school students compared to rural schools ($p<0.05$) (56), while Forsyth et al. (1999) found no difference in Temazepam use between an urban and rural school (79).

## Sexual identity

The correlation between sexual behavior and BZD misuse in young adults in the US was described in two studies (48,66).

Klare et al. (2020) showed elevated BZD misuse among sexual identity minorities (66). Gay men aged 18 to 25 years had higher rates of non-prescription BZD use compared to heterosexual men (AOR 1.91; 95% CI 1.02–3.58) (66). This article also presents that lesbian and bisexual women in this age category had higher rates of past year non-prescription use of BZD than heterosexual women (AOR 1.82; 95% CI 1.23–2.67 and AOR 1.94; 95% CI 1.40–2.69) (66).

Similar results were found by McCabe et al. (2005). College students that had been sexually active with both genders were over three times more likely to report past year BZD misuse compared to those who had been sexually active with opposite sex partners only (AOR 3.78; 95% CI 2.66–5.36) (48). Also, when evaluating lifetime non-prescription use of BZDs, they found that almost one third of all students (29,7%; $p<0.001$) who had sex with both opposite and same sex partners reported the misuse of these drugs (48).

## Public vs. private schools

Three studies investigated the difference of lifetime non-prescription use of BZDs between public and private schools in Brazil (23,27,55). In one study, no statistically significant difference in BZD misuse was found between private or public schools, while there was a significantly higher lifetime use for all drugs in those attending private schools ($p<0,05$) (23). In contrast, two other studies showed that lifetime BZD misuse was more common among students in private schools (AOR 1.47; 95% CI 1.17–1.84; AOR 1.92; 95% CI 1.69–2.18) (27,55).

## Educational status

Rickert et al. (1999) studied the differences in educational level of adolescent and young adult women (aged 14 to 26 years) engaging in BZD misuse, more specifically the use of flunitrazepam (68). When looking at school enrollment (59% vs. 56%) and repeating grades at school (32% vs. 28%), none of them were significantly different between users and nonusers of BZDs (68).

Klare et al. (2020) stated that male college students aged 18 to 25 years were less likely to misuse BZDs (66). However, non-prescription BZD use in female students was unrelated to educational attainment (66).

Likewise, Schepis et al. (2018) found that students being in school or college graduates, aged 12 to 17 and 18 to 25 years respectively, were less likely to report past year (z-)BZD misuse (12–17y: OR 0.54; 95% CI 0.42–0.70 and 18–25y: OR 0.66; 95% CI 0.59–0.73) (29).

## Socioeconomic status / insurance

One study found higher rates of having health insurance among BZD misusers, but this could not be demonstrated as statistically significant (69). Regarding social class and income, two studies of Opaleye et al. (2013 and 2014) found that lifetime non-prescribed use of sedatives/tranquilizers was more common among wealthier students (from higher social classes and from private schools) (27,55). Another study confirmed this trend, specifying that adolescents were at an increased risk for Ambien misuse (with 68%) when coming from homes with a total family income of $50,000 or more (60).

## Criminality

Liu et al. (2005) examined the abused drugs and background profiles of those arrested for drug use in Taiwan. Of those arrested on drug-related charges where BZDs were found in urine samples (18%), 4.1% were aged under 17 years and 9.4% were aged 18 to 22 years. Generally, across all ages, the profile identified for BZD users was similar to that of opiate and amphetamine users (e.g. 70% had less than 9 years of schooling, there was a male preponderance) although a higher ratio of BZD users (14%) were arrested in recreational settings (80).

Another study found that the use of flunitrazepam was positively associated with an increased level of criminal activity among youths aged 16 to 23 years (being booked or arrested past year once vs. none: AOR 3.5, 95% CI 1.9–6.5) (71). Spooner et al. (2000) also found a significant association between criminal behavior and BZD use in the univariate test, but not in their multivariate model (81).

## Screening methods

Our research did not yield any studies investigating a screening method for misuse of (z-)BZDs in young adults specifically. The methods were examined in a setting of misuse of different substances, among them (z-)BZDs. The Leeds Dependence Questionnaire (LDQ) for example, is a self-report measure of dependence that consists of 10 items but is not specific for any substance (82). Another questionnaire is CRAFFT, where ≥ 2 questions answered with ‘yes’ are associated with a higher risk of having a substance use disorder diagnosis (42,83). Falck et al. (2012) applied this questionnaire to high school students and found that higher scores on CRAFFT were associated with higher numbers of drugs ever having been used ($p<0.0001$) and currently being used ($p<0.0001$) (42). Solbergsdottir et al. (2008) compared self-report of drug use with a screening for these drugs in urine among

young people aged 15 to 24 years seeking treatment. The urine analysis used was a Fluorescence Polarization Immunoassay (FPIA) technology, while the self-report was a standardized questionnaire. For BZDs, the degree of agreement between these methods was high (84).

### Approaches

To motivate adolescents to reduce their substance misuse, a contingency management (CM) program was evaluated by Lott et al. (2009). Patients with absence of BZDs and other drugs in their urine or perfect attendance earned chances to draw from a bag of prices. Decrement of BZD-positive urine tests was noted between the control group and the CM group. However, the difference was not significant (85).

## Discussion

The aim of this review was to assemble the available literature on misuse of (z-)BZDs by children, adolescents and young adults. Our points of interest were the prevalence of misuse in this population, potential risk factors for misuse, screening methods and approaches of non-medical (z-)BZD use.

### Key findings

We noticed a remarkable limited number of studies investigating subjects aged 6 to 12 years (22–27). More specifically, no articles concerning the prevalence of misuse of (z-)BZDs were found.

For the age group of 12 to 18 years and 18 to 25 years, the discrepancy concerning lifetime and past year prevalence rates of (z-)BZD misuse is remarkable. In the first group, lifetime and past year prevalence rates vary from 1.4% to 3% and 1.9% to 2.3% respectively (28–30). In contrast to this, the rates in the second group are 19% and 13.5% respectively (29).

Previous studies showed that NMUPD is prevalent in high school students as well as in college students. (75,86,87). The lifetime prevalence rates of NMU of (z-)BZDs in high school and college students varied in our studies from 0.43% (38) to 21% (39) and from 1.1% (46) to 12.2% (44) respectively.

Although data investigating gender differences are not consistent, in most of the included studies females were more likely to report (z-)BZD misuse than their male counterparts (23,27–29,31,40,54–58). These results are in line with Votaw et al. (2019), who investigated BZD misuse (88). They also found inconsistent data concerning gender differences. The prevalence of BZD misuse varied with other additional factors. For example, the prevalence in the US was comparable between men and women, while outside the US women had a higher risk for BZD misuse compared to men (89).

Different risk factors for NMU of (z-)BZDs were discussed. Mental health problems are a recurring topic. These problems include the presence of PD, (past year) AD and (history of) mental health treatment. Except for one article, a positive correlation is seen for the different psychological issues with the highest odds for past year AD in adolescents (OR=6.54) and young adults (OR=3.18) (31,34,64,66,90). These findings are in line with research in adults, that found that psychiatric symptoms and psychiatric disorders were associated with BZD misuse

(88,91–93). In contrast to this, Schepis et al. (2018B) confirmed lower misuse odds when in presence of past year mental health treatment (OR=0,76) (29).

Both current as well as past medical use of (z-)BZDs were associated with higher rates of NMU of these drugs (29,31,43,55). (Z-)BZD misuse was also more likely to occur in people who had a friend or family member misusing these drugs (55,60,68,69,72).

It seemed that Caucasian people were more likely to engage in (z-)BZD misuse compared to other races (14,31,35,37,60,63,66,68,69,71,75,94). Similar findings were already described in older age groups by Cook et al. (2018). They concluded that Caucasians have more BZD prescription fills and are more likely to have extreme numbers of BZDs prescriptions. Subsequently, they were more likely to be diagnosed with BZD dependence than Blacks, Latinos and Asians. Racial/ethnic minorities were more likely to only have one BZD prescription, which reduces the risk of dependence (95).

Co-ingestion of other substances was more frequently reported among people misusing (z-)BZDs compared to people who used these drugs as prescribed. Both the (mis)use of legal substances and prescription stimulants as well as illegal drugs was common among (z-)BZD misusers (37,40,44,48,68,70–74).

The data on the relationship between the level of education and the misuse of (z-)BZDs is scarce. Our research contained three studies which stated that students in school or college graduates (12–25 years) were less likely to report the misuse of BZDs (29,66,68).

Our research could not identify any study investigating screening methods for (z-)BZD misuse specifically in our target age group. The already existing screening methods being described in the included studies, more specifically the LDQ and CRAFFT, were questionnaires that screened for multiple substances of misuse. One study applied this CRAFFT questionnaire specifically to high school students and obtained rates for BZDs. This study showed higher rates of BZD misuse in students with higher scores on the questionnaire (42).

Only one article concerned the approach of BZD misuse within adolescents aged 12 to 18 years. This article evaluated a CM program (85). Other studies that mentioned screening tools or approach of misuse had no substance or age specific data that met our inclusion criteria.

## Strengths and limitations

One of the strengths of this study is the broad search strategy and large number of articles (13.752) that were initially retrieved from six databases. This is because the initial aim was to perform a scoping review. After the critical assessment, 59 of the articles were found to be of good quality. This made the review more relevant and reliable. Additionally, the PRISMA 2020 checklist and the PRISMA flow diagram was used during the process which ensured a structured approach to this systematic review (21). Another strength of this study was the capacity of four reviewers, whereby every article was reviewed by one and verified by another reviewer. Disagreements were discussed with the different reviewers and a consensus was reached.

Although our review contained a large number of studies, there were some limitations. First, the most important limitation is the conversion of the study type from a scoping to a systematic review during the full text screening. Data processing of all included studies was not feasible because of the unexpected large number of studies concerning our review questions. Because we were forced to narrow our research, reporting bias may have occurred as we excluded all articles regarding overdose and poisoning. Secondly, a subdivision for age was made

based on recurring age groups found in the different studies included. However, this did not align with the division used in development psychology as written earlier (18,19). The cut-offs were set at 6 to 12, 12 to 18 and 18 to 25 years. A lack of information regarding (z-)BZD misuse in children under the age of 12 years was noticed. Therefore, we could not make a conclusion regarding this age category. Thirdly, the included studies hardly made a distinction between z-drugs and BZDs. These were regularly studied together. Furthermore, the substances studied were often not clearly defined. For example, substances were often subdivided in different categories (f.e. anxiolytics, tranquilizers sedatives) which were not further specified. Similarly, studies were excluded because of the lack of specification of the drugs that were misused (for example, named as NMUPD). Therefore, data concerning prevalence or risk factors for (z-)BZD misuse specifically could not always be retrieved and the study had to be excluded. Finally, several studies were excluded because of the use of different age categories in comparison to the one that we aimed for. If a study includes an age group with a cut-off above the age of 25 years, we could not extract data concerning our target age group.

## Hypotheses and future research

Lifetime prevalence rates of NMU of (z-)BZDs in adolescents and young adults varied a lot between studies. This could be due to different usage patterns between geographic regions. For example, different studies found higher rates of (z-)BZD misuse in Southern regions of the US (48,77,94). Differences based on continents are also suggested (46). Additionally, the variability concerning age groups and characteristics was high. Future research should focus on clear cut study designs to make comparisons and conclusions easier. Besides, another focus of interest should be the misuse of (z-)BZDs at younger ages (from 6 to 12 years), since our search did not yield any results regarding this age group. We assume misuse within this age group includes mainly a setting of poisoning, while the studies concerning this topic were excluded as mentioned above. Moreover, research in this age group is generally restricted.

For adolescents aging from 12 to 18 years, increased odds of misuse were found when older in this group, both with and without history of receiving prescriptions for multiple years (28,31). It seems reasonable to assume that it is caused by the fact that adolescence is associated with less parental monitoring, lack of decision-making, need for dissociation from their environment, need to self-regulate their negative emotions and lack of decision-making skills caused by substance abuse (8,10,11,30,96). Murphy et al. (2018) made a similar conclusion for subjects aged 18 to 25 years. They stated that they often misuse these drugs to self-regulate their emotions (11).

Due to the easier accessibility of (z-)BZDs, high levels of stress and better knowledge of the implications linked to self-medication, we assumed to find a high prevalence of NMU of (z-)BZDs in (para)medical students (52,97). We could not confirm this because of a lack of articles. Future studies to confirm this assumption would be interesting.

Different risk factors for NMU of (z-)BZDs were identified. As an illustration, it seems that females tend to engage more in NMU of (z-)BZDs than males of the same age, but no explanation was given. Psychological problems were also linked to a higher risk of this misuse. The National Institute of Mental Health and the NHLBI declared that women are at increased risk for anxiety and insomnia in comparison to men (98). Previous literature also showed that women were more likely to be prescribed BZDs than men (99). At the same time, an enhanced risk of NMU of (z-)BZDs is noted in people that have ever used these drugs for medical reasons (29,31,43,55). A

possible explanation for this is that people who received a prescription for these medications were more likely to perceive the risk associated with non-prescription use as low (27). We assume that women get more prescriptions of these medications, which makes them more prone to misuse in comparison to men. Further research is needed to confirm this assumption.

We also found an important association between NMU of (z-)BZDs and the co-ingestion with other substances (37,40,44,48,68,70–74). It is unclear whether (z-)BZD misusers are at increased risk of using other substances or if people (mis)using these substances are more likely to engage in (z-)BZD misuse. This association seems to exist in both directions when investigating opioid misuse but has to be further examined for other substances (29,48). Furthermore, co-ingestion is linked to different health risks which emphasize the importance of further research. For example, previous studies in the general population described the risks of co-ingesting BZDs with alcohol. It increases the intoxicating effects of both substances with an increased risk of overdose as a result (88,100,101).

Even though we focused mainly on the risk factors for NMU (z-)BZDs, the importance of protective factors came to our knowledge during our literature search. Ford et al. (2012) found a decreased risk of (z-)BZD misuse in presence of a strong bond to parents and to school (60). Wu et al. (2006) confirmed these findings and found a lower risk of NMU of club drugs when staying in school, being married and residing in nonmetropolitan areas (71). Religiosity also seems to be a protective factor for (z-)BZD misuse (29). Previous research also revealed that protective factors for drug abuse by adolescents can be categorized into three main domains, more specifically individual, family and community factors (102). Domains which we recognize in the protective factors that we identified. Knowledge of protective factors could be useful to health care practitioners for well-considered prescribing behavior. Therefore, future research should focus more on protective factors for the misuse of (z-)BZDs.

Although it was not a part of our research question, we could find different reasons for the misuse of (z-)BZD and other drugs in adolescents and young adults in the included articles. The main reasons that were mentioned can be divided in three categories as described by Quintero et al. (2006): self-medication (e.g. to relieve tensions and facilitate relaxation, sleep induction, to reduce mental stress, to relieve anxiety symptoms), socio-recreational applications (e.g. to get high, to have fun, for socializing and partying, for being stoned/buzz, bang or chilled; to increase in self-confidence, to sense of dissociation, to have a good time with friends) and uses organized around academic demands (e.g. prior to an examination, studying for regular exams, before attending classes) (11,44,47,53,103). Knowledge of these reasons could be useful to develop screening tools and prevention strategies for people who are at risk for NMU of (z-)BZDs.

# Conclusion

(z-)BZDS are frequently misused prescription drugs among adolescents and young adults. Evidence about the misuse of these drugs at younger ages is still scarce. While we could identify a few risk factors for NMU of (z-)BZDs, future research should further focus on other risk factors and motivations for non-medical (z-)BZD use. Additionally, research on protective factors is needed. This in order to develop suitable screening tools and intervention strategies for adolescents and young adults who are at risk for (z-)BZD misuse or who are already misusing these drugs.

# Persoonlijke reflectie

*Caroline Van de Pol*

Het proces van onze thesis verliep over het algemeen evenwichtig en volgens onze vooropgestelde planning. In het begin schrikte een groepswerk van vier personen – en bovendien mensen die ik heel goed ken – mij af, maar achteraf gezien was dit nergens voor nodig.

De keuze van het onderwerp verliep vlot. Als HAIO zijn we ons heel bewust van de risico's die verbonden zijn aan het gebruik van benzodiazepines en z-drugs. Hierdoor zijn we vaak voorzichtig en (soms te) terughoudend met het voorschrijven hiervan. Daarom leek het ons interessant om een onderzoek uit te voeren naar de prevalentie van het misbruik van deze drugs en welke factoren patiënten meer vatbaar maken voor misbruik. Bovendien zijn er weinig screeningmethoden en richtlijnen voor interventies voorhanden waarop we ons in de praktijk kunnen baseren om deze problematiek aan te pakken. Omdat jongeren deel uitmaken van een kwetsbare populatie wat betreft hun persoonlijke ontwikkeling en uitdagingen en omdat we bovendien een afbakening moesten maken wat betreft de doelgroep, hebben we specifiek op kinderen, jongeren en jongvolwassenen gefocust.

Het initiële opzet van onze thesis was een scoping review. Omdat we meer literatuur vonden dan verwacht en omwille van de combinatie met onze stage, waren we genoodzaakt om het onderzoek meer af te bakenen en besloten we ons werk te beperken tot een systematische review. In het begin viel me dit moeilijk, omdat ik perfectionistisch ben ingesteld. Daarom had ik de scoping review graag tot een goed einde gebracht en deze volledig willen uitwerken. We hebben dit in onze groep open kunnen bespreken. Op dat moment is democratisch beslist om de het onderzoeksveld te beperken, maar ik had begrip voor deze keuze en ik besefte ook dat we de thesis op deze manier tot een beter einde konden brengen. Achteraf gezien bleek dit de beste beslissing. We hebben de thesis volgens de planning kunnen afwerken en de data die we hadden hebben we heel nauwkeurig kunnen uitwerken. Dit was ons niet gelukt als we de omschakeling naar een systematische review niet gemaakt hadden. Moesten we dit niet gedaan hebben, zouden we volgens mij over het algemeen onvoldoende tijd hebben gehad om onze thesis af te werken, laat staan om de data uitgebreid en overzichtelijk uit te werken.

Al van in het begin hebben we een duidelijke planning opgesteld, die we tot op het einde bijna exact hebben kunnen volgen. Aangezien we het schrijven van deze thesis moesten combineren met onze stage, waren er regelmatig momenten waarop één of meerdere personen een drukkere periode in de praktijk doormaakten. Op die momenten konden de andere groepsleden meer werk op zich nemen. Zo heeft iedereen momenten gehad waarop er ten opzichte van de anderen meer of minder gewerkt werd aan deze thesis, maar uiteindelijk was het aandeel van elk groepslid ongeveer even groot.

Voor het uitschrijven van de inleiding, methodologie en discussie zijn we begonnen met brainstormen en hebben we deze ideeën samengevat. Van hieruit konden we dan beginnen met de globale opbouw van deze gedeeltes. Dat deden we vooral in groep. Vervolgens begon er iemand met een aanzet tot schrijven, waarop dan werd verder gewerkt door de anderen. Voor het opstellen van de zoekstrategie hebben we samen afgesproken om deze uit te werken. Aangezien we met vier waren, konden we de screening op abstract en nadien full text met kwaliteitsbeoordeling telkens in duo uitwerken. Bij onenigheid konden we beroep doen op onze andere groepsleden. Hierbij wisselden we bij een nieuwe fase regelmatig van partner, om op die manier andere inzichten te bekomen.

Het resultatengedeelte hebben we eerst opgesplitst in verschillende hoofdstukken. Deze hebben we vervolgens onderling verdeeld voor verdere uitwerking, zodat iedereen op zijn eigen tempo verder aan deze onderdelen kon werken. Nadien lazen we de delen van de andere groepsleden door zodat de schrijfstijl meer homogeen werd.
We hielden regelmatig overlegmomenten en toetsten onzekerheden en twijfels met elkaar af. Het feit dat we elkaar goed kenden heeft hier volgens mij een positieve invloed op gehad en maakte overleg laagdrempelig, waardoor we goed op elkaar waren afgestemd.
Omdat we een heel grote hoeveelheid artikels moesten verwerken, hebben we ons regelmatig afgevraagd hoe we deze informatie overzichtelijk zouden kunnen neerschrijven. We hebben tijdens het proces heel veel steun gehad aan onze co-promotor Kristien Coteur en bovendien was er regelmatig overleg met onze promotoren prof. Matheï en prof. Van Nuland. Het verschuiven van deadlines omwille van de werkdruk werd ook steeds met onze promotoren en co-promotor afgetoetst zodat we op vlak van planning niet in de problemen geraakten en de thesis tijdig konden afwerken.
Voor het verwerken van onze resultaten zijn we begonnen met het in kaart brengen van alle data in Excel, ook telkens per twee. Nadien zijn we vanuit dit overzicht begonnen met de verschillende onderverdelingen, bv wat betreft prevalentie in de verschillende leeftijdscategorieën en risicofactoren. Op die manier kreeg de structuur van onze thesis vorm en ook het nut van ons onderzoek werd duidelijker.
Uiteindelijk hebben we geconcludeerd dat het misbruik van benzodiazepines en z-drugs prevalent is, hoewel cijfers uiteenlopen tussen verschillende artikels. Studies over misbruik in België lijken mij zinvol om het onderzoek nog meer te kunnen toepassen in onze praktijk. Bovendien hebben we een aantal duidelijke risicofactoren kunnen identificeren die voorbeschikken tot misbruik. Zo was een van onze bevindingen dat personen die in het verleden een voorschrift kregen, een groter risico hebben op misbruik. Dit is een aandachtspunt dat we zeker kunnen meenemen naar de praktijk. Tot slot bevestigt ons onderzoek wat we zelf ook al aanvoelden, namelijk dat er maar weinig screeningstools en interventiestrategieën voorhanden zijn om dit misbruik aan te pakken of te voorkomen.

## References


1. Lader M. Benzodiazepines revisited-will we ever learn? Addiction. 2011 Dec;106(12):2086–109.
2. Dell'osso B, Lader M. Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal. Vol. 28, European Psychiatry. 2013. p. 7–20.
3. Sidorchuk A, Isomura K, Molero Y, Hellner C, Lichtenstein P, Chang Z, et al. Benzodiazepine prescribing for children, adolescents, and young adults from 2006 through 2013: A total population register-linkage study. PLoS Medicine. 2018 Aug 1;15(8).
4. Zito JM, Safer DJ, DosReis S, Gardner JF, Magder L, Soeken K, et al. Psychotropic practice patterns for youth: A 10-year perspective. Archives of Pediatrics and Adolescent Medicine. 2003;157(1):17–25.
5. Bushnell GA, Crystal S, Olfson M. Prescription Benzodiazepine Use in Privately Insured U.S. Children and Adolescents. American Journal of Preventive Medicine. 2019 Dec 1;57(6):775–85.
6. Mctague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Vol. 2018, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2018.
7. Patel V, Flisher AJ, Hetrick S, Mcgorry P. Series Mental health of young people: a global public-health challenge. www.thelancet.com [Internet]. 2007;369. Available from: www.thelancet.com
8. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of. Arch Gen Psychiatry [Internet]. 2005;62(June):593–602. Available from: http://archpsyc.jamanetwork.com /article.aspx ?doi=10.1001/archpsyc.62.6.593
9. McDonagh MS, Holmes R, Hsu F. Pharmacologic Treatments for Sleep Disorders in Children: A Systematic Review. Journal of Child Neurology. 2019 Apr 1;34(5):237–47.
10. Peters RJ, Meshack AF, Kelder SH, Webb P, Smith D, Garner K. Alprazolam (Xanax®) use among southern youth: Beliefs and social norms concerning dangerous rides on "handlebars." Journal of Drug Education. 2007;37(4):417–28.
11. Murphy KD, Lambert S, McCarthy S, Sahm LJ, Byrne S. "You Don't Feel": The Experience of Youth Benzodiazepine Misuse in Ireland. Journal of Psychoactive Drugs. 2018 Mar 15;50(2):121–8.
12. Boeuf-Cazou O, Bongue B, Ansiau D, Marquié JC, Lapeyre-Mestre M. Impact of long-term benzodiazepine use on cognitive functioning in young adults: The VISAT cohort. European Journal of Clinical Pharmacology. 2011 Oct;67(10):1045–52.
13. Stranks EK, Crowe SF. The acute cognitive effects of zopiclone, zolpidem, zaleplon, and eszopiclone: A systematic review and meta-analysis. Journal of Clinical and Experimental Neuropsychology. 2014 Aug 20;36(7):691–700.
14. Schepis TS. Age Cohort differences in the nonmedical use of prescription Zolpidem: Findings from a nationally representative sample. Addictive Behaviors. 2014;39(9):1311–7.
15. Bouvier BA, Waye KM, Elston B, Hadland SE, Green TC, Marshall BDL. Prevalence and correlates of benzodiazepine use and misuse among young adults who use prescription opioids non-medically. Drug and Alcohol Dependence. 2018 Feb 1;183:73–7.

16. Jensen PS, Bhatara VS, Vitiello B, Hoagwood K, Feil M, Burke LB. Psychoactive medication prescribing practices for U.S. Children: Gaps between research and clinical practice. J Am Acad Child Adolesc Psychiatry. 1999;38(5):557–65.
17. Witek MW, Rojas V, Alonso C, Minami H, Silva RR. Review of Benzodiazepine use in Children and Adolescents. Psychiatric Quarterly [Internet]. 2005 Oct;76(3):283–96. Available from: http://link.springer.com/10.1007/s11126-005-2982-5
18. Whitbourne SK. Life Span Development: A Six-Unit Lesson Plan for High School Psychology Teachers. 2012;
19. Shaffer DR, Kipp K. Developmental Psychology: Childhood and Adolescence. seventh edition. Thomson WadsWorth; 2007. 5 p.
20. National Heart L and BI. Study Quality Assessment Tools | NHLBI, NIH [Internet]. [cited 2022 Apr 19]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools
21. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Revista Espanola de Nutricion Humana y Dietetica. 2016;20(2):148–60.
22. Arditti J, Spadari M, Camprasse MA, Dalecky C, Bourdon JH. Usage abusif des produits psychoactifs licites ou illicites chez l'enfant et l'adolescent dans la région PACA (Sud-Est de la France). In: Therapie. ADIS International Ltd; 2004. p. 595–7.
23. Guimarães JL, Godinho PH, Cruz R, Kappann I, Alves L, Junior T. Psychoactive drugs use by school-age adolescents, Brazil. Rev Saúde Pública [Internet]. 2004;38(1). Available from: www.fsp.usp.br/rspGuimarãesJLetal
24. Carter YH, Robson WJ. Drug misuse in adolescence. Archives of Emergency Medicine. 1987;4(1):17–24.
25. Noto AR, Nappo SA, Galduróz JCF, Mattei R, Carlini EA. Use of drugs among street children in Brazil. Journal of Psychoactive Drugs. 1997;29(2):185–92.
26. Sharma S, Sharma2 G, Barkataki1 B. Family and Social Factors as Predictors of Drug Misuse and Delinquent Behavior in Juveniles [Internet]. Vol. 22, International Medical Journal. 2015. Available from: www.who.inl/
27. Opaleye ES, Ferri CP, Locatelli DP, Amato TC, Noto AR. Nonprescribed use of tranquilizers and use of other drugs among Brazilian students. Revista Brasileira de Psiquiatria. 2014;36(1):16–23.
28. Rigg KK, Ford JA. The misuse of benzodiazepines among adolescents: Psychosocial risk factors in a national sample. Drug and Alcohol Dependence. 2014;137(1):137–42.
29. Schepis TS, Teter CJ, Simoni-Wastila L, McCabe SE. Prescription tranquilizer/sedative misuse prevalence and correlates across age cohorts in the US. Addictive Behaviors. 2018 Dec 1;87:24–32.
30. McCauley JL, Danielson CK, Amstadter AB, Ruggiero KJ, Resnick HS, Hanson RF, et al. The role of traumatic event history in non-medical use of prescription drugs among a nationally representative sample of US adolescents. Journal of Child Psychology and Psychiatry and Allied Disciplines. 2010 Jan;51(1):84–93.
31. Boyd CJ, Austic E, Epstein-Ngo Q, Veliz PT, McCabe SE. A prospective study of adolescents' nonmedical use of anxiolytic and sleep medication. Vol. 29, Psychology of Addictive Behaviors. Educational Publishing Foundation; 2015. p. 184–91.
32. Kashif Shabbir M, Fatima K, Anwar S. A Study To Assess The Harmfulness Of Benzodiazepine Use Among Medical Students With Respect To Gender. Age, Locality & Monthly Income, Indo Am J P Sci [Internet]. 2018;2018(12):17180–5. Available from: http://doi.org/10.5281/zenodo.2528525

33. Kurtz SP, Surratt HL, Buttram ME, Levi-Minzi MA, Chen M. Interview as intervention: The case of young adult multidrug users in the club scene. Journal of Substance Abuse Treatment. 2013 Apr;44(3):301–8.
34. Kurtz SP, Buttram ME, Surratt HL. Benzodiazepine Dependence among Young Adult Participants in the Club Scene Who Use Drugs. Journal of Psychoactive Drugs. 2017 Jan 1;49(1):39–46.
35. Viana AG, Trent L, Tull MT, Heiden L, Damon JD, Hight TL, et al. Non-medical use of prescription drugs among Mississippi youth: Constitutional, psychological, and family factors. Addictive Behaviors. 2012 Dec;37(12):1382–8.
36. Levine SB, Coupey SM. Nonmedical Use of Prescription Medications: An Emerging Risk Behavior Among Rural Adolescents. Journal of Adolescent Health. 2009 Apr;44(4):407–9.
37. McCabe SE, Boyd CJ, Young A. Medical and Nonmedical Use of Prescription Drugs among Secondary School Students. Journal of Adolescent Health. 2007 Jan;40(1):76–83.
38. Juan W, Jian-Xiong D, Lan G, Yuan H, Xue G, Jing-Hui H, et al. Non-medical use of psychoactive drugs in relation to suicide tendencies among Chinese adolescents. Addictive Behaviors. 2015 Dec 1;51:31–7.
39. Gana MK, Njodi IA. The impact of prevalence of substance abuse among secondary school students in Borno State, Nigeria. Indian Journal of Public Health Research and Development. 2019 Jul 1;10(6):1407–11.
40. McCabe SE, West BT. Medical and nonmedical use of prescription benzodiazepine anxiolytics among U.S. high school seniors. Addictive Behaviors. 2014;39(5):959–64.
41. Mccabe SE, West BT, Cranford JA, Ross-Durow P, Young A, Teter CJ, et al. Medical Misuse of Controlled Medications Among Adolescents. Vol. 165, Arch Pediatr Adolesc Med. 2011.
42. Falck RS, Ramzi Nahhas MW, Robert Carlson MG. Surveying Teens in School to Assess the Prevalence of Problematic Drug Use. Journal of School Health. 2012;82(5):217–24.
43. Parks KA, Frone MR, Muraven M. The Role of Past and Current Medical Use on Nonmedical Use of Prescription Drugs among College Students: Exploring Same-Drug and Cross-Drug Class Associations. Substance Use and Misuse. 2020 Aug 3;55(11):1759–64.
44. Brandt SA, Taverna EC, Hallock RM. A survey of nonmedical use of tranquilizers, stimulants, and pain relievers among college students: Patterns of use among users and factors related to abstinence in non-users. Drug and Alcohol Dependence. 2014;143(1):272–6.
45. Benotsch EG, Martin AM, Koester S, Mason MJ, Jeffers AJ, Snipes DJ. Driving under the influence of prescription drugs used nonmedically: Associations in a young adult sample. Substance Abuse. 2015 Jan 2;36(1):99–105.
46. Olashore AA, Ogunwobi O, Totego E, Opondo PR. Psychoactive substance use among first-year students in a Botswana University: Pattern and demographic correlates. BMC Psychiatry. 2018 Aug 31;18(1).
47. Marin GH, Cañas M, Carlson S, Silvestrini P, Corva S, Mestorino N, et al. Self-Medication, Substance Abuse and Alcohol Consumption in Students Attending to. Original Article. 2010;29(8):1425–55.
48. McCabe SE. Correlates of nonmedical use of prescription benzodiazepine anxiolytics: Results from a national survey of U.S. college students. Drug and Alcohol Dependence. 2005 Jul 1;79(1):53–62.

49. Kushwaha RP, Rauniar GP, Koirala B, Mandal NK. Prevalence of Substance Use among Undergraduate Students in a Medical College of Nepal. Journal of the Nepal Medical Association. 2019 Jan 1;57(219):315–9.
50. Maddux JF, Hoppe SK, Costello RM. Psychoactive Substance Use among Medical Students. American Journal of Psychiatry. 1986;143(2):187–91.
51. Paredes NP, Miasso AI, Tirapelli CR. Consumption of benzodiazepines without prescription among first-year nursing students at the university of guayaquil, school of nursing, Ecuador. Revista Latino-Americana de Emfermagem [Internet]. 2008;16(especial):634–9. Available from: www.eerp.usp.br/rlae
52. Balayssac D, Pereira B, Darfeuille M, Cuq P, Vernhet L, Collin A, et al. Use of psychotropic medications and illegal drugs, and related consequences among French pharmacy students - SCEP study: A nationwide cross-sectional study. Frontiers in Pharmacology. 2018 Jul 17;9(JUL).
53. Dube KC, Kumar A, Kumar N, Gupta SP. Prevalence and pattern of drug use amongst college students. Vol. 57. 1978.
54. Carrasco-Garrido P, Jiménez-Trujillo I, Hernández-Barrera V, Lima Florencio L, Palacios-Ceña D. Patterns of non-medical use of benzodiazepines and Z-Drugs among adolescents and young adults: gender differences and related factors. Journal of Substance Use. 2021;26(2):190–6.
55. Opaleye ES, Noto AR, Sanchez ZM, Amato TC, Locatelli DP, Gossop M, et al. Nonprescribed use of tranquilizers or sedatives by adolescents: a Brazilian national survey [Internet]. 2013. Available from: http://www.biomedcentral.com/1471-2458/13/499
56. Adelekan ML. Self-reported drug use among secondary school students in the Nigerian State of Ogun. Bull Narc. 1989;41(1–2):109–16.
57. Currie CL, Wild C. Adolescent Use of Prescription Drugs to Get High in Canada [Internet]. Vol. 57, The Canadian Journal of Psychiatry. 2012. Available from: www.TheCJP.ca
58. Rezahosseini O, Roohbakhsh A, Tavakolian V, Assar S. Drug Abuse among University Students of Rafsanjan, Iran. Iranian Journal of Psychiatry and Behavioral Sciences [Internet]. 2014 [cited 2022 Apr 20];8(2):81. Available from: /pmc/articles/PMC4105608/
59. Bouvier BA, Waye KM, Elston B, Hadland SE, Green TC, Marshall BDL. Prevalence and correlates of benzodiazepine use and misuse among young adults who use prescription opioids non-medically. Drug and Alcohol Dependence [Internet]. 2018 Feb;183(October 2017):73–7. Available from: https://doi.org/10.1016/j.drugalcdep.2017.10.023
60. Ford JA, McCutcheon J. The misuse of Ambien among adolescents: Prevalence and correlates in a national sample. Addictive Behaviors. 2012 Dec;37(12):1389–94.
61. Gazibara T, Milic M, Parlic M, Stevanovic J, Lazic D, Maric G, et al. Illict drug use and academia in North Kosovo: Prevalence, patterns, predictors and health-related quality of life. PLoS ONE. 2018 Jul 1;13(7).
62. Nevadomsky J. Patterns of self-reported drug use among secondary school students in Bendel State, Nigeria. Bulletin of Narcotics. 1981;33(1):9–19.
63. Whiteside LK, Walton MA, Bohnert ASB, Blow FC, Bonar EE, Ehrlich P, et al. Nonmedical prescription opioid and sedative use among adolescents in the emergency department. Pediatrics. 2013 Nov 1;132(5):825–32.
64. Zullig KJ, Divin AL. The association between non-medical prescription drug use, depressive symptoms, and suicidality among college students. Addictive Behaviors. 2012 Aug;37(8):890–9.

65. Sandi L, Diaz A, Uglade F. Drug use and associated factors among rural adolescents in Costa Rica. Substance Use and Misuse. 2002;37(5–7).
66. Klare DL, McCabe SE, Ford JA, Schepis TS. Prescription drug misuse, other substance use, and sexual identity: The significance of educational status and psychological distress in US young adults. Substance Abuse. 2020;1–11.
67. Schepis TS, West BT, Teter CJ, McCabe SE. Prevalence and correlates of co-ingestion of prescription tranquilizers and other psychoactive substances by U.S. high school seniors: Results from a national survey. Addictive Behaviors. 2016 Jan 1;52:8–12.
68. Rickert VI, Wiemann CM, Berenson AB. Prevalence, Patterns, and Correlates of Voluntary Flunitrazepam Use [Internet]. 1999. Available from: http://www.pediatrics.org/cgi/content/full/103/1/e6
69. Stone AM, Merlo LJ. Psychiatric medication-seeking beliefs and behaviors among college students. American Journal of Drug and Alcohol Abuse. 2012 Jul;38(4):314–21.
70. Best DW, Barrie A. Impact of illicit substance activity on young people. Journal of Substance Use. 1997;2(4):197–202.
71. Wu LT, Schlenger WE, Galvin DM. Concurrent use of methamphetamine, MDMA, LSD, ketamine, GHB, and flunitrazepam among American youths. Drug and Alcohol Dependence. 2006 Sep 1;84(1):102–13.
72. Pedersen W, Lavik NJ. Adolescents and benzodiazepines: prescribed use, self-medication and intoxication. Acta Psychiatrica Scandinavica. 1991;84(1):94–8.
73. McCabe SE, Cranford JA. Motivational subtypes of nonmedical use of prescription medications: Results from a national study. Journal of Adolescent Health. 2012 Nov;51(5):445–52.
74. Dåderman AM, Edman G, Meurling AW, Levander S, Kristiansson M. Flunitrazepam intake in male offenders. Nordic Journal of Psychiatry. 2012 Apr;66(2):131–40.
75. McCabe SE, West BT, Teter CJ, Boyd CJ. Trends in medical use, diversion, and nonmedical use of prescription medications among college students from 2003 to 2013: Connecting the dots. Addictive Behaviors. 2014;39(7):1176–82.
76. Rickert VI, Wiemann CM, Berenson AB. Communications in Brief Flunitrazepam: More Than a Date Rape Drug. Vol. 13, J Pediatr Adolesc Gynecol. 2000.
77. Sheridan DC, Hendrickson RG, Beauchamp G, Laurie A, Fu R, Horowitz BZ. Adolescent Intentional Abuse Ingestions Overall 10-Year Trends and Regional Variation [Internet]. 2016. Available from: www.pec-online.com
78. Murphy KD, Byrne S, Sahm LJ, Lambert S, Mccarthy S. Use of addiction treatment services by Irish youth: does place of residence matter? Rural and Remote Health [Internet]. 2014;14(2735):online. Available from: http://www.rrh.org.auAvailable:http://www.rrh.org.au
79. Forsyth AJM, Barnard M. Contrasting levels of adolescent drug use between adjacent urban and rural communities in Scotland. Vol. 94, Addiction. 1999.
80. Liu C, Tsay W ing, Hsu J. Drug Use and Profile of Individuals Arrested on Drug-related Charges in Taiwan.
81. Spooner C, Mattick RP, Nofs W. A study of the patterns and correlates of substance use among adolescents applying for drug treatment. Australian and New Zealand Journal of Public Health. 2000;24(5):492–502.
82. Kelly JF, Magill M, Slaymaker V, Kahler C. Psychometric validation of the Leeds Dependence Questionnaire (LDQ) in a young adult clinical sample. Addictive Behaviors. 2010 Apr;35(4):331–6.
83. Oesterle TS, Hitschfeld MJ, Lineberry TW, Schneekloth TD. CRAFFT as a substance use screening instrument for adolescent psychiatry admissions. Journal of Psychiatric Practice. 2015 Jul 1;21(4):259–66.

84. Solbergsdottir E, Bjornsson G, Gudmundsson LS, Tyrfingsson T, Kristinsson J. Validity of Self-Reports and Drug Use among Young People Seeking Treatment for Substance Abuse or Dependence. Journal of Addictive Diseases. 2004;23(1):29–38.
85. Lott DC, Jencius S. Effectiveness of very low-cost contingency management in a community adolescent treatment program. Drug and Alcohol Dependence. 2009 Jun 1;102(1–3):162–5.
86. Lipari RN. Monthly variation in Substance Use Initiation among Full-time College Students. The CBHSQ Report. 2015.
87. Center for Behavioral Health Statistics S. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings [Internet]. 2014. Available from: http://store.samhsa.gov/home.
88. Votaw VR, Geyer R, Rieselbach MM, McHugh RK. The epidemiology of benzodiazepine misuse: A systematic review. Vol. 200, Drug and Alcohol Dependence. Elsevier Ireland Ltd; 2019. p. 95–114.
89. Center for Behavioral Health Statistics S. Results from the 2017 National Survey on Drug Use and Health: Detailed Results. 2018.
90. Schepis TS. Age Cohort differences in the nonmedical use of prescription Zolpidem: Findings from a nationally representative sample. Addictive Behaviors [Internet]. 2014;39(9):1311–7. Available from: http://dx.doi.org/10.1016/j.addbeh.2014.04.018
91. Abrahamsson T, Berglund M, Håkansson A. Non-Medical Prescription Drug Use (NMPDU) and Poor Quality of Life in the Swedish General Population. The American Journal of Addictions. 2014;24:271–7.
92. Goodwin RD, Hasin DS. Sedative use and misuse in the United States. Addiction. 2002;555–62.
93. Martins SS, Gorelick DA. Conditional substance abuse and dependence by diagnosis of mood or anxiety disorder or schizophrenia in the U.S. population. Drug and Alcohol Dependence. 2011 Dec 1;119(1–2):28–36.
94. Mccabe SE, Knight JR, Teter CJ, Wechsler H. Non-medical use of prescription stimulants among US college students: prevalence and correlates from a national survey. 2005;
95. Cook B, Creedon T, Wang Y, Lu C, Carson N, Jules P, et al. Examining racial/ethnic differences in patterns of benzodiazepine prescription and misuse. Drug and Alcohol Dependence. 2018 Jun 1;187:29–34.
96. Patel V, Flisher AJ, Hetrick S, McGorry P. Mental health of young people: a global public-health challenge. Lancet. 2007;369(9569):1302–13.
97. Khanal P, Ghimire RH, Gautam B, Dhungana SK, Parajuli P, Jaiswal AK, et al. Substance use among medical students in Kathmandu valley - PubMed. Journal of the Nepal Medical Association [Internet]. 2010 [cited 2022 Apr 19];50(180):267–72. Available from: https://pubmed.ncbi.nlm.nih.gov/22049888/
98. National Institute on Drug Abuse. Substance Use in Women Research Report. 2020.
99. Agarwal SD, Landon BE. Patterns in Outpatient Benzodiazepine Prescribing in the United States. JAMA Netw Open. 2019 Jan 4;2(1):e187399.
100. Schmitz A. Benzodiazepine use, misuse, and abuse: A review. Mental Health Clinician. 2016 Jan 1;6(3):120–6.
101. Koski A, Ojanperä I, Vuori E. Interaction of alcohol and drugs in fatal poisonings. Human and Experimental Toxicology. 2003 May 1;22(5):281–7.
102. Nawi AM, Ismail R, Ibrahim F, Hassan MR, Manaf MRA, Amit N, et al. Risk and protective factors of drug abuse among adolescents: a systematic review. BMC Public Health. 2021 Dec 1;21(1).

103. Quintero G, Peterson J, Young B. An exploratory study of socio-cultural factors contributing to prescription drug misuse among college students. Journal of Drug Issues. 2006;36(4):903–32.

# Appendix A

**Search Strategy**

| | |
|---|---|
| **Pubmed** | **Concept 1:**<br><br>("benzodiazepines"[MeSH] OR benzodiazepin*[tiab] OR alprazolam[tiab] OR anthramycin*[tiab] OR bromazepam[tiab] OR Brotizolam[tiab] OR diazepam[tiab] OR flumazenil[tiab] OR flunitrazepam[tiab] OR flurazepam[tiab] OR lorazepam[tiab] OR nitrazepam[tiab] OR oxazepam[tiab] OR pirenzepin*[tiab] OR prazepam[tiab] OR temazepam[tiab] OR clonazepam[tiab] OR devazepide[tiab] OR Chlorazepate[tiab] OR Clotiazepam[tiab] OR Cloxazolam[tiab] OR ethyl-loflazepate[tiab] OR ketazolam[tiab] OR loprazolam[tiab] OR lormetazepam[tiab] OR nordazepam[tiab] OR estazolam[tiab] OR medazepam[tiab] OR midazolam[tiab] OR olanzapin*[tiab] OR triazolam[tiab] OR "zolpidem"[MeSH] OR zolpidem[tiab] OR SL-800750[tiab] OR SL-80-0750[tiab] OR zolirin*[tiab] OR "zolpi lich"[tiab] OR zolpinox[tiab] OR zolpimist[tiab] OR ambien[tiab] OR amsic[tiab] OR bikalm[tiab] OR stilnoct[tiab] OR stilnox[tiab] OR dalparan[tiab] OR zodormdura[tiab] OR zoldem[tiab] OR "eszopiclone"[MeSH] OR eszopiclon*[tiab] OR lunesta[tiab] OR lunivia[tiab] OR estorra[tiab] OR "zopiclone"[Supplementary Concept] OR zopiclon*[tiab] OR zop[tiab] OR zopicalma[tiab] OR zopiclodura[tiab] OR zopitan[tiab] OR zorclon*[tiab] OR imovan*[tiab] OR ximovan*[tiab] OR zimovan*[tiab] OR limovan*[tiab] OR optidorm[tiab] OR rhovan*[tiab] OR siaten[tiab] OR somnosan[tiab] OR zileze[tiab] OR zomiclon*[tiab] OR "zopi puren"[tiab] OR zopicalm[tiab] OR "zaleplon"[Supplementary Concept] OR zaleplon*[tiab] OR zelepion*[tiab] OR starnoc[tiab] OR sonata[tiab] OR "Z drug*"[tiab] OR esopiclon*[tiab] OR zimoclon*[tiab] OR L-846[tiab] OR SK-1041[tiab] OR andante[tiab] OR hegon[tiab] OR hipnodem[tiab] OR noctiplon*[tiab] OR plenidon*[tiab] OR zaplon*[tiab] OR zerene[tiab] OR adinazolam[tiab] OR Deracyn[tiab] OR Bretazenil[tiab] OR camazepam[tiab] OR Chlordiazepoxid*[tiab] OR Chlordiazepoxyd*[tiab] OR Dealkylflurazepam[tiab] OR desalkylflurazepam[tiab] OR norflurazepam[tiab] OR delorazepam[tiab] OR fludiazepam[tiab] OR flutoprazepam[tiab] OR Halazepam[tiab] OR Ativan[tiab] OR meclonazepam[tiab] OR dormicum[tiab] OR nimetazepam[tiab] OR norclobazam[tiab] OR nordiazepam[tiab] OR pagoclon*[tiab] OR phenazepam[tiab] OR pinazepam[tiab] OR quazepam[tiab] OR Tetrazepam[tiab] OR myolastan[tiab] OR Zapizolam[tiab] OR Diclazepam[tiab] OR Cloniprazepam[tiab] OR Flubromazepam[tiab] OR Clonazolam[tiab] OR Pyrazolam[tiab] OR Flubromazolam[tiab] OR Etizolam[tiab] OR Nitemazepam[tiab] OR Bromazolam[tiab] OR Flualprazolam[tiab] OR Flunitrazolam[tiab] OR Nitrazolam[tiab] OR Deschloretizolam[tiab] OR Metizolam[tiab] OR Fluclotizolam[tiab] OR Cinazepam[tiab] OR Nifoxipam[tiab] OR "designer benzo*"[tiab] OR "happy 5"[tiab] OR "happy five"[tiab] OR erimin[tiab] OR "rohypnol"[tiab] OR versed[tiab] OR trilam[tiab] OR clobazam[tiab] OR clorazepate[tiab])<br><br>**Concept 2:**<br><br>("Adolescent"[MeSH] OR adolescen*[tiab] OR teen*[tiab] OR youth*[tiab] OR preteen*[tiab] OR juvenile[tiab] OR "child"[mh:noexp] OR child*[tiab] OR "Minors"[Mesh] OR minors[tiab] OR "Pediatrics"[mh:noexp] OR pediatr*[tiab] OR paediatr*[tiab] OR "Puberty"[mh:noexp] OR pubert*[tiab] OR pubescen*[tiab] OR prepuber*[tiab] OR prepubescen*[tiab] OR "students"[mh:noexp] OR student*[tiab] OR "elementary pupil*"[tiab] OR "schools"[mh:noexp] OR school*[tiab] OR "educational institution*"[tiab] OR college[tiab] OR "universities"[Mesh] OR universities[tiab] OR university[tiab] OR "young adult"[MeSH] OR "younger adult*"[tiab] OR "young adult*"[tiab] OR "prime adult*"[tiab] OR "young people"[tiab] OR "young person*"[tiab] OR junior*[tiab] OR kid[tiab] OR kids[tiab] OR youngster*[tiab] OR "child psychiatry"[mh:noexp] OR "age 12"[tiab] OR "ages 12"[tiab] OR "age 15"[tiab] OR "ages 15"[tiab] OR "age 16"[tiab] OR "ages 16"[tiab] OR "ages 18"[tiab] OR "age 18"[tiab] OR "ages 21"[tiab] OR "age 21"[tiab] OR "12 years"[tiab] OR "15 years"[tiab] OR "16 years"[tiab] OR "18 years"[tiab] OR "21 years"[tiab] OR "aged 12"[tiab] OR "aged 15"[tiab] OR "aged 16"[tiab] OR "aged 18"[tiab] OR "aged 21"[tiab])<br><br>**Concept 3:**<br><br>("drug misuse"[MeSH] OR misus*[tiab] OR "mis us*"[tiab] OR "non medical us*"[tiab] OR "nonmedical us*"[tiab] OR NMUPD[tiab] OR overdos*[tiab] OR "over dos*"[tiab] OR overus*[tiab] OR "over us*"[tiab] OR overutilization*[tiab] OR overutilisation*[tiab] OR "over utilisation*"[tiab] OR "over utilization*"[tiab] OR "Behavior, addictive"[mh:noexp] OR addict*[tiab] OR "addiction medicine"[Mesh] OR "substance-related disorders"[mh:noexp] OR "substance related disorder*"[tiab] OR dependenc*[tiab] OR "drug facilitation"[tiab] OR "drug habituation"[tiab] OR toxicoman*[tiab] OR abuse*[tiab] OR abusing[tiab] OR abusage[tiab] OR abusable[tiab] OR "drug problem*"[tiab] OR "substance abuse, oral"[mh:noexp] OR intoxic*[tiab] OR intoxification[tiab] OR "poisoning"[mh:noexp] OR poisoning*[tiab] OR "toxic |

| | |
|---|---|
| | injur*”[tiab] OR toxicosis[tiab] OR toxicoses[tiab] OR “drug overdose”[mh:noexp] OR “drug emergenc*”[tiab] OR “outpatient utilization”[tiab] OR (outpatients[tiab] AND (utilisation[tiab] OR utilization[tiab])) OR “outpatient utilisation”[tiab] OR "Outpatients"[Mesh] OR “outpatients us*”[tiab] OR “outpatient us*”[tiab] OR “outpatient benzodiazepine”[tiab] OR “harmful us*”[tiab] OR “use disorder*”[tiab]) |
| **Embase** | **Concept 1:**<br><br>(‘benzodiazepine derivative’/de OR ‘benzodiazepine’/exp OR ‘benzodiazepin*’:ti,ab,kw OR 'benzodiazepine receptor stimulating agent'/de OR ‘alprazolam’/de OR ‘alprazolam’:ti,ab,kw OR ‘anthramycin’/de OR ‘anthramycin*’:ti,ab,kw OR ‘bromazepam’/de OR ‘bromazepam’:ti,ab,kw OR ‘brotizolam’:ti,ab,kw OR ‘clonazepam’/de OR ‘clonazepam’:ti,ab,kw OR ‘devazepide’/de OR ‘devazepide’:ti,ab,kw OR ‘diazepam’/de OR ‘diazepam’:ti,ab,kw OR ‘nordazepam’/de OR ‘nordazepam’:ti,ab,kw OR ‘flumazenil’/de OR ‘flumazenil’:ti,ab,kw OR ‘flunitrazepam’/de OR ‘flunitrazepam’:ti,ab,kw OR ‘flurazepam’/de OR ‘flurazepam’:ti,ab,kw OR ‘lorazepam’/de OR ‘lorazepam’:ti,ab,kw OR ‘nitrazepam’/de OR ‘nitrazepam’:ti,ab,kw OR ‘oxazepam’/de OR ‘oxazepam’:ti,ab,kw OR ‘pirenzepine’/de OR ‘pirenzepin*’:ti,ab,kw OR ‘prazepam’/de OR ‘prazepam’:ti,ab,kw OR ‘temazepam’/de OR ‘temazepam’:ti,ab,kw OR ‘chlordiazepoxide’/de OR ‘clotiazepam’:ti,ab,kw OR ‘cloxazolam’:ti,ab,kw OR ‘clobazam’/de OR ‘clobazam’:ti,ab,kw OR ‘ethyl loflazepate’/de OR ‘ethyl loflazepate’:ti,ab,kw OR ‘ketazolam’:ti,ab,kw OR ‘loprazolam’:ti,ab,kw OR ‘lormetazepam’/de OR ‘lormetazepam’:ti,ab,kw OR ‘clorazepate’/de OR ‘clorazepate’:ti,ab,kw OR ‘chlorazepate’:ti,ab,kw OR ‘estazolam’/de OR ‘estazolam’:ti,ab,kw OR ‘medazepam’/de OR ‘medazepam’:ti,ab,kw OR ‘midazolam’/de OR ‘midazolam’:ti,ab,kw OR ‘olanzapine’:ti,ab,kw OR ‘versed’:ti,ab,kw OR ‘dormicum':ti,ab,kw OR ‘triazolam’/de OR ‘triazolam’:ti,ab,kw OR ‘trilam':ti,ab,kw OR ‘zolpidem’/de OR ‘zolpidem’:ti,ab,kw OR ‘SL-800750’:ti,ab,kw OR ‘SL-80-0750’:ti,ab,kw OR ‘zolirin*’:ti,ab,kw OR ‘zolpi lich’:ti,ab,kw OR ‘zolpinox’:ti,ab,kw OR ‘zolpimist’:ti,ab,kw OR ‘ambien’:ti,ab,kw OR ‘amsic’:ti,ab,kw OR ‘bikalm’:ti,ab,kw OR ‘stilnoct’:ti,ab,kw OR ‘stilnox’:ti,ab,kw OR ‘dalparan’:ti,ab,kw OR ‘zodormdura’:ti,ab,kw OR ‘zoldem’:ti,ab,kw OR ‘eszopiclone’/de OR ‘eszopiclon*’:ti,ab,kw OR ‘lunesta’:ti,ab,kw OR ‘estorra’:ti,ab,kw OR ‘lunivia’:ti,ab,kw OR ‘zopiclone’/de OR ‘zopiclon*’:ti,ab,kw OR ‘zop’:ti,ab,kw OR ‘zopicalma’:ti,ab,kw OR ‘zopiclodura’:ti,ab,kw OR ‘zopitan*’:ti,ab,kw OR ‘zorclon*’:ti,ab,kw OR ‘imovan*’:ti,ab,kw OR ‘ximovan*’:ti,ab,kw OR ‘zimovan*’:ti,ab,kw OR ‘limovan*’:ti,ab,kw OR ‘optidorm’:ti,ab,kw OR ‘rhovan*’:ti,ab,kw OR ‘siaten’:ti,ab,kw OR ‘somnosan’:ti,ab,kw OR ‘zileze’:ti,ab,kw OR ‘zomiclon*’:ti,ab,kw OR ‘zopi-puren’:ti,ab,kw OR ‘zopicalm’:ti,ab,kw OR ‘zaleplon’/de OR ‘zaleplon*’:ti,ab,kw OR ‘zelepion*’:ti,ab,kw OR ‘starnoc’:ti,ab,kw OR ‘sonata’:ti,ab,kw OR ‘z drug’/exp OR ‘z drug*’:ti,ab,kw OR ‘esopiclon*’:ti,ab,kw OR ‘zimoclon*’:ti,ab,kw OR ‘L-846’:ti,ab,kw OR ‘SK-1041’:ti,ab,kw OR ‘andante’:ti,ab,kw OR ‘hegon’:ti,ab,kw OR ‘hipnodem’:ti,ab,kw OR ‘noctiplon*’:ti,ab,kw OR ‘plenidon*’:ti,ab,kw OR ‘zaplon*’:ti,ab,kw OR ‘zerene’:ti,ab,kw OR ‘adinazolam’:ti,ab,kw OR ‘Deracyn’:ti,ab,kw OR ‘Bretazenil’:ti,ab,kw OR ‘camazepam’:ti,ab,kw OR ‘Chlordiazepoxid*’:ti,ab,kw OR ‘Chlordiazepoxyd*’:ti,ab,kw OR ‘Dealkylflurazepam’:ti,ab,kw OR ‘desalkylflurazepam’:ti,ab,kw OR ‘norflurazepam’:ti,ab,kw OR ‘delorazepam’:ti,ab,kw OR ‘fludiazepam’:ti,ab,kw OR ‘flutoprazepam’:ti,ab,kw OR ‘Halazepam’:ti,ab,kw OR ‘Ativan’:ti,ab,kw OR ‘meclonazepam’:ti,ab,kw OR ‘dormicum’:ti,ab,kw OR ‘nimetazepam’:ti,ab,kw OR ‘norclobazam’:ti,ab,kw OR ‘nordiazepam’:ti,ab,kw OR ‘pagoclon*’:ti,ab,kw OR ‘phenazepam’:ti,ab,kw OR ‘pinazepam’:ti,ab,kw OR ‘quazepam’:ti,ab,kw OR ‘Tetrazepam’:ti,ab,kw OR ‘myolastan’:ti,ab,kw OR ‘Zapizolam’:ti,ab,kw OR ‘Diclazepam’:ti,ab,kw OR ‘Cloniprazepam’:ti,ab,kw OR ‘Flubromazepam’:ti,ab,kw OR ‘Clonazolam’:ti,ab,kw OR ‘Pyrazolam’:ti,ab,kw OR ‘Flubromazolam’:ti,ab,kw OR ‘Etizolam’:ti,ab,kw OR ‘Nitemazepam’:ti,ab,kw OR ‘Bromazolam’:ti,ab,kw OR ‘Flualprazolam’:ti,ab,kw OR ‘Flunitrazolam’:ti,ab,kw OR ‘Nitrazolam’:ti,ab,kw OR ‘Deschloretizolam’:ti,ab,kw OR ‘Metizolam’:ti,ab,kw OR ‘Fluclotizolam’:ti,ab,kw OR ‘Cinazepam’:ti,ab,kw OR ‘Nifoxipam’:ti,ab,kw OR ‘designer benzo*’:ti,ab,kw OR ‘happy 5’:ti,ab,kw OR ‘happy five’:ti,ab,kw OR ‘erimin’:ti,ab,kw OR ‘rohypnol’:ti,ab,kw OR ‘benzodiazepine dependence’/de)<br><br>**Concept 2:**<br><br>(‘adolescent’/exp OR ‘adolescen*’:ti,ab,kw OR ‘adolescence’/de OR ‘teen*’:ti,ab,kw OR ‘youth*’:ti,ab,kw OR ‘preteen*’:ti,ab,kw OR ‘juvenile’/de OR ‘juvenile’:ti,ab,kw OR ‘child’/de OR ‘child*’:ti,ab,kw OR ‘childhood’/de OR ‘minors’:ti,ab,kw OR ‘pediatrics’/de OR ‘pediatr*’:ti,ab,kw OR ‘paediatr*’:ti,ab,kw OR ‘Puberty’/de OR ‘pubert*’:ti,ab,kw OR ‘pubescen*’:ti,ab,kw OR ‘prepuber*’:ti,ab,kw OR ‘prepuberty’/exp OR ‘prepubescen*’:ti,ab,kw OR ‘student’/de OR ‘student*’:ti,ab,kw OR ‘school’/de OR ‘school*’:ti,ab,kw OR ‘educational institution*’:ti,ab,kw OR ‘elementary pupil*’:ti,ab,kw OR ‘college’/de OR ‘college’:ti,ab,kw OR ‘university’/exp OR ‘universities’:ti,ab,kw OR ‘university’:ti,ab,kw OR ‘young adult’/exp OR ‘younger adult*’:ti,ab,kw OR ‘young adult*’:ti,ab,kw OR ‘prime adult*’:ti,ab,kw OR ‘young people’:ti,ab,kw OR ‘young person*’:ti,ab,kw OR ‘junior*’:ti,ab,kw OR ‘kid’:ti,ab,kw OR ‘kids’:ti,ab,kw OR ‘school child’/exp OR ‘youngster*’:ti,ab,kw OR ‘child psychiatry’/de OR ‘age 12’:ti,ab,kw OR ‘ages |

| | |
|---|---|
| | 12':ti,ab,kw OR 'age 15':ti,ab,kw OR 'ages 15':ti,ab,kw OR 'age 16':ti,ab,kw OR 'ages 16':ti,ab,kw OR 'ages 18':ti,ab,kw OR 'age 18':ti,ab,kw OR 'ages 21':ti,ab,kw OR 'age 21':ti,ab,kw OR '12 years':ti,ab,kw OR '15 years':ti,ab,kw OR '16 years':ti,ab,kw OR '18 years':ti,ab,kw OR '21 years':ti,ab,kw OR 'aged 12':ti,ab,kw OR 'aged 15':ti,ab,kw OR 'aged 16':ti,ab,kw OR 'aged 18':ti,ab,kw OR 'aged 21':ti,ab,kw)<br><br>**Concept 3:**<br><br>('drug misuse'/exp OR 'misuse*':ti,ab,kw OR 'mis-us*':ti,ab,kw OR 'non medical us*':ti,ab,kw OR 'nonmedical us*':ti,ab,kw OR 'NMUPD':ti,ab,kw OR 'overdos*':ti,ab,kw OR 'over dos*':ti,ab,kw OR 'overus*':ti,ab,kw OR 'over us*':ti,ab,kw OR 'overutilization*':ti,ab,kw OR 'overutilisation*':ti,ab,kw OR 'over utilization*':ti,ab,kw OR 'over utilisation*':ti,ab,kw OR 'addiction'/de OR 'addiction medicine'/exp OR 'drug dependence'/de OR 'dependenc*':ti,ab,kw OR 'addict*':ti,ab,kw OR 'drug facilitation':ti,ab,kw OR 'drug habituation':ti,ab,kw OR 'substance related disorder*':ti,ab,kw OR 'toxicoman*':ti,ab,kw OR 'benzodiazepine dependence'/de OR 'abuse'/de OR 'abuse*':ti,ab,kw OR 'abusing':ti,ab,kw OR 'abusage':ti,ab,kw OR 'abusable':ti,ab,kw OR 'drug problem*':ti,ab,kw OR 'substance abuse'/de OR 'drug abuse'/de OR 'multiple drug abuse'/de OR 'intoxication'/de OR 'intoxic*':ti,ab,kw OR 'intoxification':ti,ab,kw OR 'poisoning*':ti,ab,kw OR 'toxic injur*':ti,ab,kw OR 'toxicosis':ti,ab,kw OR 'toxicoses':ti,ab,kw OR 'drug overdose'/de OR 'drug intoxication'/de OR 'drug emergenc*':ti,ab,kw OR 'outpatient'/exp OR 'outpatient utilization':ti,ab,kw OR 'outpatients utilization':ti,ab,kw OR 'outpatient utilisation':ti,ab,kw OR 'outpatients utilisation':ti,ab,kw OR 'outpatients us*':ti,ab,kw OR 'outpatient us*':ti,ab,kw OR 'outpatient benzodiazepine':ti,ab,kw OR 'harmful us*':ti,ab,kw OR 'use disorder*':ti,ab,kw) |
| **CINAHL** | **Concept 1:**<br><br>(MH "Antianxiety Agents, Benzodiazepine+") OR (MH "Zolpidem") OR (MH "Eszopiclone") OR (MH "Sedatives, Nonbarbiturate+") OR AB("benzodiazepin*" OR "alprazolam" OR "anthramycin*" OR "bromazepam" OR "brotizolam" OR "clonazepam" OR "devazepide" OR "diazepam" OR "nordazepam" OR "flumazenil" OR "flunitrazepam" OR "flurazepam" OR "lorazepam" OR "nitrazepam" OR "oxazepam" OR "pirenzepin*" OR "prazepam" OR "temazepam" OR "clotiazepam" OR "cloxazolam" OR "clobazam" OR "ethyl loflazepate" OR "ketazolam" OR "loprazolam" OR "lormetazepam" OR "clorazepate" OR "chlorazepate" OR "estazolam" OR "medazepam" OR "midazolam" OR "olanzapine" OR "versed" OR "dormicum" OR "triazolam" OR "trilam" OR "zolpidem" OR "SL-800750" OR "SL-80-0750" OR "zolirin*" OR "zolpi lich" OR "zolpinox" OR "zolpimist" OR "ambien" OR "amsic" OR "bikalm" OR "stilnoct" OR "stilnox" OR "dalparan" OR "zodormdura" OR "zoldem" OR "eszopiclon*" OR "lunesta" OR "estorra" OR "lunivia" OR "zopiclon*" OR "zop" OR "zopicalma" OR "zopiclodura" OR "zopitan*" OR "zorclon*" OR "imovan*" OR "ximovan*" OR "zimovan*" OR "limovan*" OR "optidorm" OR "rhovan*" OR "siaten" OR "somnosan" OR "zileze" OR "zomiclon*" OR "zopi-puren" OR "zopicalm" OR "zaleplon*" OR "zelepion*" OR "starnoc" OR "sonata" OR "z drug*" OR "esopiclon*" OR "zimoclon*" OR "L-846" OR "SK-1041" OR "andante" OR "hegon" OR "hipnodem" OR "noctiplon*" OR "plenidon*" OR "zaplon*" OR "zerene" OR "adinazolam" OR "Deracyn" OR "Bretazenil" OR "camazepam" OR "Chlordiazepoxid*" OR "Chlordiazepoxyd*" OR "Dealkylflurazepam" OR "desalkylflurazepam" OR "norflurazepam" OR "delorazepam" OR "fludiazepam" OR "flutoprazepam" OR "Halazepam" OR "Ativan" OR "meclonazepam" OR "dormicum" OR "nimetazepam" OR "norclobazam" OR "nordiazepam" OR "pagoclon*" OR "phenazepam" OR "pinazepam" OR "quazepam" OR "Tetrazepam" OR "myolastan" OR "Zapizolam" OR "Diclazepam" OR "Cloniprazepam" OR "Flubromazepam" OR "Clonazolam" OR "Pyrazolam" OR "Flubromazolam" OR "Etizolam" OR "Nitemazepam" OR "Bromazolam" OR "Flualprazolam" OR "Flunitrazolam" OR "Nitrazolam" OR "Deschloretizolam" OR "Metizolam" OR "Fluclotizolam" OR "Cinazepam" OR "Nifoxipam" OR "designer benzo*" OR "happy 5" OR "happy five" OR "erimin" OR "rohypnol") OR TI("benzodiazepin*" OR "alprazolam" OR "anthramycin*" OR "bromazepam" OR "brotizolam" OR "clonazepam" OR "devazepide" OR "diazepam" OR "nordazepam" OR "flumazenil" OR "flunitrazepam" OR "flurazepam" OR "lorazepam" OR "nitrazepam" OR "oxazepam" OR "pirenzepin*" OR "prazepam" OR "temazepam" OR "clotiazepam" OR "cloxazolam" OR "clobazam" OR "ethyl loflazepate" OR "ketazolam" OR "loprazolam" OR "lormetazepam" OR "clorazepate" OR "chlorazepate" OR "estazolam" OR "medazepam" OR "midazolam" OR "olanzapine" OR "versed" OR "dormicum" OR "triazolam" OR "trilam" OR "zolpidem" OR "SL-800750" OR "SL-80-0750" OR "zolirin*" OR "zolpi lich" OR "zolpinox" OR "zolpimist" OR "ambien" OR "amsic" OR "bikalm" OR "stilnoct" OR "stilnox" OR "dalparan" OR "zodormdura" OR "zoldem" OR "eszopiclon*" OR "lunesta" OR "estorra" OR "lunivia" OR "zopiclon*" OR "zop" OR "zopicalma" OR "zopiclodura" OR "zopitan*" OR "zorclon*" OR "imovan*" OR "ximovan*" OR "zimovan*" OR "limovan*" OR "optidorm" OR "rhovan*" OR "siaten" OR "somnosan" OR "zileze" OR "zomiclon*" OR "zopi-puren" OR "zopicalm" OR "zaleplon*" OR "zelepion*" OR "starnoc" OR "sonata" OR "z drug*" OR "esopiclon*" OR "zimoclon*" OR "L-846" OR "SK-1041" OR "andante" OR "hegon" OR "hipnodem" OR "noctiplon*" OR "plenidon*" OR "zaplon*" OR "zerene" OR "adinazolam" OR "Deracyn" OR "Bretazenil" OR "camazepam" OR "Chlordiazepoxid*" OR "Chlordiazepoxyd*" OR "Dealkylflurazepam" OR "desalkylflurazepam" OR "norflurazepam" OR "delorazepam" OR "fludiazepam" OR "flutoprazepam" OR "Halazepam" OR |

| | |
|---|---|
| | "Ativan" OR "meclonazepam" OR "dormicum" OR "nimetazepam" OR "norclobazam" OR "nordiazepam" OR "pagoclon*" OR "phenazepam" OR "pinazepam" OR "quazepam" OR "Tetrazepam" OR "myolastan" OR "Zapizolam" OR "Diclazepam" OR "Cloniprazepam" OR "Flubromazepam" OR "Clonazolam" OR "Pyrazolam" OR "Flubromazolam" OR "Etizolam" OR "Nitemazepam" OR "Bromazolam" OR "Flualprazolam" OR "Flunitrazolam" OR "Nitrazolam" OR "Deschloretizolam" OR "Metizolam" OR "Fluclotizolam" OR "Cinazepam" OR "Nifoxipam" OR "designer benzo*" OR "happy 5" OR "happy five" OR "erimin" OR "rohypnol")<br><br>**Concept 2:**<br><br>(MH "Child") OR (MH "Adolescence") OR (MH "Minors (Legal)") OR (MH "Pediatrics") OR (MH "Puberty") OR (MH "Students, High School") OR (MH "High School Graduates") OR (MH "Schools, Secondary") OR (MH "Students, College") OR (MH "Schools") OR (MH "Colleges and Universities") OR (MH "Schools, Middle") OR (MH "Schools, Elementary") OR (MH "College Graduates") OR (MH "Young Adult") OR (MH "Adult Children") OR (MH "Child Psychiatry") OR AB("adolescen*" OR "teen*" OR "youth*" OR "preteen*" OR "juvenile" OR "child*" OR "minors" OR "pediatr*" OR "paediatr*" OR "pubert*" OR "pubescen*" OR "prepuber*" OR "prepubescen*" OR "student*" OR "school*" OR "educational institution*" OR "elementary pupil*" OR "college" OR "universities" OR "university" OR "younger adult*" OR "young adult*" OR "prime adult*" OR "young people" OR "young person*" OR "junior*" OR "kid" OR "kids" OR "youngster*" OR "age 12" OR "ages 12" OR "age 15" OR "ages 15" OR "age 16" OR "ages 16" OR "ages 18" OR "age 18" OR "ages 21" OR "age 21" OR "12 years" OR "15 years" OR "16 years" OR "18 years" OR "21 years" OR "aged 12" OR "aged 15" OR "aged 16" OR "aged 18" OR "aged 21") OR TI("adolescen*" OR "teen*" OR "youth*" OR "preteen*" OR "juvenile" OR "child*" OR "minors" OR "pediatr*" OR "paediatr*" OR "pubert*" OR "pubescen*" OR "prepuber*" OR "prepubescen*" OR "student*" OR "school*" OR "educational institution*" OR "elementary pupil*" OR "college" OR "universities" OR "university" OR "younger adult*" OR "young adult*" OR "prime adult*" OR "young people" OR "young person*" OR "junior*" OR "kid" OR "kids" OR "youngster*" OR "age 12" OR "ages 12" OR "age 15" OR "ages 15" OR "age 16" OR "ages 16" OR "ages 18" OR "age 18" OR "ages 21" OR "age 21" OR "12 years" OR "15 years" OR "16 years" OR "18 years" OR "21 years" OR "aged 12" OR "aged 15" OR "aged 16" OR "aged 18" OR "aged 21")<br><br>**Concept 3:**<br><br>(MH "Substance Dependence") OR (MH "Substance Abuse") OR (MH "Overdose") OR (MH "Behavior, Addictive") OR (MH "Substance Use Disorders+") OR (MH "Poisoning") OR (MH "Addictions Nursing") OR (MH "Outpatients") OR AB("misuse*" OR "mis-us*" OR "non medical us*" OR "nonmedical us*" OR "NMUPD" OR "overdos*" OR "over dos*" OR "overus*" OR "over us*" OR "overutilization*" OR "overutilisation*" OR "over utilization*" OR "over utilisation*" OR "dependenc*" OR "addict*" OR "drug facilitation" OR "drug habituation" OR "substance related disorder*" OR "toxicoman*" OR "abuse*" OR "abusing" OR "abusage" OR "abusable" OR "drug problem*" OR "intoxic*" OR "intoxification" OR "poisoning*" OR "toxic injur*" OR "toxicosis" OR "toxicoses" OR "drug emergenc*" OR "outpatient utilization" OR "outpatients utilization" OR "outpatient utilisation" OR "outpatients utilisation" OR "outpatients us*" OR "outpatient us*" OR "outpatient benzodiazepine" OR "harmful us*" OR "use disorder*") OR TI("misuse*" OR "mis-us*" OR "non medical us*" OR "nonmedical us*" OR "NMUPD" OR "overdos*" OR "over dos*" OR "overus*" OR "over us*" OR "overutilization*" OR "overutilisation*" OR "over utilization*" OR "over utilisation*" OR "dependenc*" OR "addict*" OR "drug facilitation" OR "drug habituation" OR "substance related disorder*" OR "toxicoman*" OR "abuse*" OR "abusing" OR "abusage" OR "abusable" OR "drug problem*" OR "intoxic*" OR "intoxification" OR "poisoning*" OR "toxic injur*" OR "toxicosis" OR "toxicoses" OR "drug emergenc*" OR "outpatient utilization" OR "outpatients utilization" OR "outpatient utilisation" OR "outpatients utilisation" OR "outpatients us*" OR "outpatient us*" OR "outpatient benzodiazepine" OR "harmful us*" OR "use disorder*") |
| **Cochrane** | **Concept 1:**<br><br>[mh "Benzodiazepines"] OR [mh "Zolpidem"] OR [mh "Eszopiclone"]<br><br>OR<br><br>(benzodiazepin* OR alprazolam OR anthramycin* OR bromazepam OR brotizolam OR clonazepam OR devazepide OR diazepam OR nordazepam OR flumazenil OR flunitrazepam OR flurazepam OR lorazepam OR nitrazepam OR oxazepam OR pirenzepin* OR prazepam OR temazepam OR clotiazepam OR cloxazolam OR clobazam OR (ethyl NEXT loflazepate) OR ketazolam OR loprazolam OR lormetazepam OR clorazepate OR chlorazepate OR estazolam OR medazepam OR midazolam OR olanzapine OR versed OR dormicum OR triazolam OR trilam OR zolpidem OR (SL NEXT 800750) OR (SL NEXT 80 NEXT 0750) OR zolirin* OR (zolpi NEXT lich) OR zolpinox OR zolpimist OR ambien OR amsic OR bikalm OR stilnoct OR stilnox OR dalparan OR zodormdura OR zoldem OR eszopiclon* OR lunesta OR estorra OR lunivia OR zopiclon* OR zop OR zopicalma OR zopiclodura OR zopitan* OR zorclon* OR imovan* OR |

| | |
|---|---|
| | ximovan* OR zimovan* OR limovan* OR optidorm OR rhovan* OR siaten OR somnosan OR zileze OR zomiclon* OR (zopi NEXT puren) OR zopicalm OR zaleplon* OR zelepion* OR starnoc OR sonata OR (z NEXT drug*) OR esopiclon* OR zimoclon* OR (L NEXT 846) OR (SK NEXT 1041) OR andante OR hegon OR hipnodem OR noctiplon* OR plenidon* OR zaplon* OR zerene OR adinazolam OR Deracyn OR Bretazenil OR camazepam OR Chlordiazepoxid* OR Chlordiazepoxyd* OR Dealkylflurazepam OR desalkylflurazepam OR norflurazepam OR delorazepam OR fludiazepam OR flutoprazepam OR Halazepam OR Ativan OR meclonazepam OR dormicum OR nimetazepam OR norclobazam OR nordiazepam OR pagoclon* OR phenazepam OR pinazepam OR quazepam OR Tetrazepam OR myolastan OR Zapizolam OR Diclazepam OR Cloniprazepam OR Flubromazepam OR Clonazolam OR Pyrazolam OR Flubromazolam OR Etizolam OR Nitemazepam OR Bromazolam OR Flualprazolam OR Flunitrazolam OR Nitrazolam OR Deschloretizolam OR Metizolam OR Fluclotizolam OR Cinazepam OR Nifoxipam OR (designer NEXT benzo*) OR (happy NEXT 5) OR (happy NEXT five) OR erimin OR rohypnol):ti,ab,kw<br><br>**Concept 2:**<br><br>[mh "Adolescent"] OR [mh ^"child"] OR [mh "Minors"] OR [mh ^"pediatrics"] OR [mh ^"puberty"] OR [mh ^"students"] OR [mh ^"schools"] OR [mh "universities"] OR [mh "young adult"] OR [mh ^"child psychiatry"]<br><br>OR<br><br>(adolescen* OR teen* OR youth* OR preteen* OR juvenile OR child* OR minors OR pediatr* OR paediatr* OR pubert* OR pubescen* OR prepuber* OR prepubescen* OR student* OR school* OR (educational NEXT institution*) OR (elementary NEXT pupil*) OR college OR universities OR university OR (younger NEXT adult*) OR (prime NEXT adult*) OR (young NEXT (adult* OR people OR person*)) OR junior* OR kid OR kids OR youngster* OR ((age OR ages OR aged) NEXT (12 OR 15 OR 16 OR 18 OR 21)) OR ((12 OR 15 OR 16 OR 18 OR 21) NEXT years)):ti,ab,kw<br><br>**Concept 3:**<br><br>[mh "drug misuse"] OR [mh ^"behavior, addictive"] OR [mh "addiction medicine"] OR [mh ^"substance-related disorders"] OR [mh ^"substance abuse, oral"] OR [mh ^"poisoning"] OR [mh ^"drug overdose"] OR [mh ^"outpatients"]<br><br>OR<br><br>(misuse* OR (mis NEXT us*) OR (non NEXT medical NEXT us*) OR (nonmedical NEXT us*) OR NMUPD OR overdos* OR (over NEXT dos*) OR overus* OR overutilization* OR overutilisation* (over NEXT utilization*) OR (over NEXT utilisation*) OR dependenc* OR addict* OR (drug NEXT facilitation) OR (drug NEXT habituation) OR (substance NEXT related disorder*) OR toxicoman* OR abuse* OR abusing OR abusage OR abusable OR (drug NEXT problem*) OR intoxic* OR intoxification OR poisoning* OR (toxic NEXT injur*) OR toxicosis OR toxicoses OR (drug NEXT emergenc*) OR ((outpatient OR outpatients) NEXT (utilization OR utilization OR us* OR benzodiazepine)) OR (harmful NEXT us*) OR (use NEXT disorder*)):ti,ab,kw |
| **Web of Science** | **Concept 1:**<br><br>TS=("benzodiazepin*" OR "alprazolam" OR "anthramycin*" OR "bromazepam" OR "brotizolam" OR "clonazepam" OR "devazepide" OR "diazepam" OR "nordazepam" OR "flumazenil" OR "flunitrazepam" OR "flurazepam" OR "lorazepam" OR "nitrazepam" OR "oxazepam" OR "pirenzepin*" OR "prazepam" OR "temazepam" OR "clotiazepam" OR "cloxazolam" OR "clobazam" OR "ethyl loflazepate" OR "ketazolam" OR "loprazolam" OR "lormetazepam" OR "clorazepate" OR "chlorazepate" OR "estazolam" OR "medazepam" OR "midazolam" OR "olanzapine" OR "versed" OR "dormicum" OR "triazolam" OR "trilam" OR "zolpidem" OR "SL-800750" OR "SL-80-0750" OR "zolirin*" OR "zolpi lich" OR "zolpinox" OR "zolpimist" OR "ambien" OR "amsic" OR "bikalm" OR "stilnoct" OR "stilnox" OR "dalparan" OR "zodormdura" OR "zoldem" OR "eszopiclon*" OR "lunesta" OR "estorra" OR "lunivia" OR "zopiclon*" OR "zop" OR "zopicalma" OR "zopiclodura" OR "zopitan*" OR "zorclon*" OR "imovan*" OR "ximovan*" OR "zimovan*" OR "limovan*" OR "optidorm" OR "rhovan*" OR "siaten" OR "somnosan" OR "zileze" OR "zomiclon*" OR "zopi-puren" OR "zopicalm" OR "zaleplon*" OR "zelepion*" OR "starnoc" OR "sonata" OR "z drug*" OR "esopiclon*" OR "zimoclon*" OR "L-846" OR "SK-1041" OR "andante" OR "hegon" OR "hipnodem" OR "noctiplon*" OR "plenidon*" OR "zaplon*" OR "zerene" OR "adinazolam" OR "Deracyn" OR "Bretazenil" OR "camazepam" OR "Chlordiazepoxid*" OR "Chlordiazepoxyd*" OR "Dealkylflurazepam" OR "desalkylflurazepam" OR "norflurazepam" OR "delorazepam" OR "fludiazepam" OR "flutoprazepam" OR "Halazepam" OR "Ativan" OR "meclonazepam" OR "dormicum" OR "nimetazepam" OR "norclobazam" OR "nordiazepam" OR "pagoclon*" OR "phenazepam" OR "pinazepam" OR "quazepam" OR "Tetrazepam" OR "myolastan" OR "Zapizolam" OR "Diclazepam" OR "Cloniprazepam" OR "Flubromazepam" OR "Clonazolam" OR |

| | |
|---|---|
| | "Pyrazolam" OR "Flubromazolam" OR "Etizolam" OR "Nitemazepam" OR "Bromazolam" OR "Flualprazolam" OR "Flunitrazolam" OR "Nitrazolam" OR "Deschloretizolam" OR "Metizolam" OR "Fluclotizolam" OR "Cinazepam" OR "Nifoxipam" OR "designer benzo*" OR "happy 5" OR "happy five" OR "erimin" OR "rohypnol")<br><br>**Concept 2:**<br><br>TS=("adolescen*" OR "teen*" OR "youth*" OR "preteen*" OR "juvenile" OR "child*" OR "minors" OR "pediatr*" OR "paediatr*" OR "pubert*" OR "pubescen*" OR "prepuber*" OR "prepubescen*" OR "student*" OR "school*" OR "educational institution*" OR "elementary pupil*" OR "college" OR "universities" OR "university" OR "younger adult*" OR "young adult*" OR "prime adult*" OR "young people" OR "young person*" OR "junior*" OR "kid" OR "kids" OR "youngster*" OR "age 12" OR "ages 12" OR "age 15" OR "ages 15" OR "age 16" OR "ages 16" OR "ages 18" OR "age 18" OR "ages 21" OR "age 21" OR "12 years" OR "15 years" OR "16 years" OR "18 years" OR "21 years" OR "aged 12" OR "aged 15" OR "aged 16" OR "aged 18" OR "aged 21")<br><br>**Concept 3:**<br><br>TS=("misuse*" OR "mis-us*" OR "non medical us*" OR "nonmedical us*" OR "NMUPD" OR "overdos*" OR "over dos*" OR "overus*" OR "over us*" OR "overutilization*" OR "overutilisation*" OR "over utilization*" OR "over utilisation*" OR "dependenc*" OR "addict*" OR "drug facilitation" OR "drug habituation" OR "substance related disorder*" OR "toxicoman*" OR "abuse*" OR "abusing" OR "abusage" OR "abusable" OR "drug problem*" OR "intoxic*" OR "intoxification" OR "poisoning*" OR "toxic injur*" OR "toxicosis" OR "toxicoses" OR "drug emergenc*" OR "outpatient utilization" OR "outpatients utilization" OR "outpatient utilisation" OR "outpatients utilisation" OR "outpatients us*" OR "outpatient us*" OR "outpatient benzodiazepine" OR "harmful us*" OR "use disorder*") |
| **Psyc-Articles** | **Concept 1:**<br><br>MAINSUBJECT.EXACT.EXPLODE("Benzodiazepines") OR AB,TI("benzodiazepin*" OR "alprazolam" OR "anthramycin*" OR "bromazepam" OR "brotizolam" OR "clonazepam" OR "devazepide" OR "diazepam" OR "nordazepam" OR "flumazenil" OR "flunitrazepam" OR "flurazepam" OR "lorazepam" OR "nitrazepam" OR "oxazepam" OR "pirenzepin*" OR "prazepam" OR "temazepam" OR "clotiazepam" OR "cloxazolam" OR "clobazam" OR "ethyl loflazepate" OR "ketazolam" OR "loprazolam" OR "lormetazepam" OR "clorazepate" OR "chlorazepate" OR "estazolam" OR "medazepam" OR "midazolam" OR "olanzapine" OR "versed" OR "dormicum" OR "triazolam" OR "trilam" OR "zolpidem" OR "SL-800750" OR "SL-80-0750" OR "zolirin*" OR "zolpi lich" OR "zolpinox" OR "zolpimist" OR "ambien" OR "amsic" OR "bikalm" OR "stilnoct" OR "stilnox" OR "dalparan" OR "zodormdura" OR "zoldem" OR "eszopiclon*" OR "lunesta" OR "estorra" OR "lunivia" OR "zopiclon*" OR "zop" OR "zopicalma" OR "zopiclodura" OR "zopitan*" OR "zorclon*" OR "imovan*" OR "ximovan*" OR "zimovan*" OR "limovan*" OR "optidorm" OR "rhovan*" OR "siaten" OR "somnosan" OR "zileze" OR "zomiclon*" OR "zopi-puren" OR "zopicalm" OR "zaleplon*" OR "zelepion*" OR "starnoc" OR "sonata" OR "z drug*" OR "esopiclon*" OR "zimoclon*" OR "L-846" OR "SK-1041" OR "andante" OR "hegon" OR "hipnodem" OR "noctiplon*" OR "plenidon*" OR "zaplon*" OR "zerene" OR "adinazolam" OR "Deracyn" OR "Bretazenil" OR "camazepam" OR "Chlordiazepoxid*" OR "Chlordiazepoxyd*" OR "Dealkylflurazepam" OR "desalkylflurazepam" OR "norflurazepam" OR "delorazepam" OR "fludiazepam" OR "flutoprazepam" OR "Halazepam" OR "Ativan" OR "meclonazepam" OR "dormicum" OR "nimetazepam" OR "norclobazam" OR "nordiazepam" OR "pagoclon*" OR "phenazepam" OR "pinazepam" OR "quazepam" OR "Tetrazepam" OR "myolastan" OR "Zapizolam" OR "Diclazepam" OR "Cloniprazepam" OR "Flubromazepam" OR "Clonazolam" OR "Pyrazolam" OR "Flubromazolam" OR "Etizolam" OR "Nitemazepam" OR "Bromazolam" OR "Flualprazolam" OR "Flunitrazolam" OR "Nitrazolam" OR "Deschloretizolam" OR "Metizolam" OR "Fluclotizolam" OR "Cinazepam" OR "Nifoxipam" OR "designer benzo*" OR "happy 5" OR "happy five" OR "erimin" OR "rohypnol")<br><br>**Concept 2:**<br><br>MAINSUBJECT.EXACT("Early Adolescence") OR MAINSUBJECT.EXACT("Pediatrics") OR MAINSUBJECT.EXACT("College Students") OR MAINSUBJECT.EXACT("Elementary School Students") OR MAINSUBJECT.EXACT("Middle School Students") OR MAINSUBJECT.EXACT("Students") OR MAINSUBJECT.EXACT("Primary School Students") OR MAINSUBJECT.EXACT("Preschool Students") OR MAINSUBJECT.EXACT("High School Students") OR MAINSUBJECT.EXACT("Graduate Students") OR MAINSUBJECT.EXACT("Junior College Students") OR MAINSUBJECT.EXACT("Emerging Adulthood") OR MAINSUBJECT.EXACT("Child Psychiatry") OR MAINSUBJECT.EXACT.EXPLODE("Schools") OR MAINSUBJECT.EXACT("Colleges") OR AB,TI("adolescen*" OR "teen*" OR "youth*" OR "preteen*" OR "juvenile" OR "child*" OR "minors" OR "pediatr*" OR "paediatr*" OR "pubert*" OR "pubescen*" |

| | |
|---|---|
| | OR “prepuber*” OR “prepubescen*” OR “student*” OR “school*” OR “educational institution*” OR “elementary pupil*” OR “college” OR “universities” OR “university” OR “younger adult*” OR “young adult*” OR “prime adult*” OR “young people” OR “young person*” OR “junior*” OR “kid” OR “kids” OR “youngster*” OR “age 12” OR “ages 12” OR “age 15” OR “ages 15” OR “age 16” OR “ages 16” OR “ages 18” OR “age 18” OR “ages 21” OR “age 21” OR “12 years” OR “15 years” OR “16 years” OR “18 years” OR “21 years” OR “aged 12” OR “aged 15” OR “aged 16” OR “aged 18” OR “aged 21”)<br><br>**Concept 3:**<br><br>MAINSUBJECT.EXACT.EXPLODE("Drug Usage") OR MAINSUBJECT.EXACT("Prescription Drug Misuse") OR MAINSUBJECT.EXACT("Substance Use Disorder") OR MAINSUBJECT.EXACT("Addiction") OR MAINSUBJECT.EXACT("Drug Addiction") OR MAINSUBJECT.EXACT("Drug Usage") OR MAINSUBJECT.EXACT("Drug Dependency") OR MAINSUBJECT.EXACT("Drug Abuse") OR MAINSUBJECT.EXACT("Toxic Disorders") OR MAINSUBJECT.EXACT("Drug Overdoses") OR MAINSUBJECT.EXACT("Outpatients") OR AB,TI(“misuse*” OR “mis-us*” OR “non medical us*” OR “nonmedical us*” OR “NMUPD” OR “overdos*” OR “over dos*” OR “overus*” OR “over us*” OR “overutilization*” OR “overutilisation*” OR “over utilization*” OR “over utilisation*” OR “dependenc*” OR “addict*” OR “drug facilitation” OR “drug habituation” OR “substance related disorder*” OR “toxicoman*” OR “abuse*” OR “abusing” OR “abusage” OR “abusable” OR “drug problem*” OR “intoxic*” OR “intoxification” OR “poisoning*” OR “toxic injur*” OR “toxicosis” OR “toxicoses” OR “drug emergenc*” OR “outpatient utilization” OR “outpatients utilization” OR “outpatient utilisation” OR “outpatients utilisation” OR “outpatients us*” OR “outpatient us*” OR “outpatient benzodiazepine” OR “harmful us*” OR “use disorder*”) |

# Appendix B

**Quality Assessment According to the Tool of 'Nhlbi'** *(NIH National Heart, Lung and Blood Institute. Study Quality Assessment Tools [Internet]. Last updated July 2021. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools)*

| Author \ Question* | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Quality rating |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adejoh (2020) | Yes | Yes | No | Yes | No | Yes | Yes | NA | Yes | NA | Yes | NR | No | No | Fair |
| Adelekan (1989) | Yes | Yes | Yes | Yes | No | Yes | NA | NA | Yes | NA | Yes | NR | No | No | Fair |
| Arditti (2004) | Yes | Yes | NA | Yes | No | NA | NA | Yes | NA | NA | Yes | NR | Yes | NA | Fair |
| Balayssac (2018) | Yes | Yes | No | Yes | Yes | NA | NA | NA | Yes | NA | Yes | NR | NA | Yes | Fair |
| Baselga (1972) | No | Yes | Yes | Yes | No | Yes | NA | No | Yes | NA | No | NR | No | No | Poor |
| Bashir (2015) | Yes | Yes | Yes | Yes | No | Yes | NA | NA | NA | NA | Yes | NR | NA | No | Fair |
| Benotsch (2015) | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NA | Yes | NR | NR | Yes | Good |
| Best (2009) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | No | Good |
| Bjarneboe (1987) | No | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NA | Yes | NR | NA | Yes | Good |
| Bouvier (2018) | Yes | Yes | Yes | Yes | No | Yes | NA | No | Yes | NA | Yes | NR | No | No | Fair |
| Boyd (2015) | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | Yes | Yes | NA | Yes | Yes | Good |
| Brandt (2014) | Yes | Yes | No | Yes | No | Yes | Yes | NA | Yes | No | Yes | NR | No | No | Fair |
| Busto (1981) | Yes | Yes | Yes | Yes | No | Yes | Yes | NA | Yes | NA | Yes | NR | NR | No | Good |
| Busto (1996) | Yes | Yes | Yes | Yes | Yes | Yes | NA | Yes | Yes | NA | Yes | NR | NA | No | Good |
| Cakici (2018) | Yes | Yes | Yes | Yes | Yes | Yes | NA | NA | Yes | NA | Yes | NR | No | No | Good |
| Carrasco-garrido (2020) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | Yes | Good |
| Carter (1987) | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NA | Yes | NR | NA | No | Fair |
| Christophersen (1990) | Yes | No | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NA | NA | No | Fair |
| Croen (1997) | Yes | No | Yes | Yes | No | Yes | Yes | No | Yes | Yes | Yes | NR | No | No | Fair |
| Currie (2012) | Yes | Yes | Yes | Yes | Yes | Yes | NA | Yes | Yes | No | Yes | NR | No | No | Good |
| Daderman (2012) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | NA | Yes | NR | NA | Yes | Good |
| Darbishire (2019) | Yes | No | Yes | Yes | No | Yes | NA | NA | NA | NA | Yes | NA | No | NA | Poor |
| Dube (1978) | Yes | No | Yes | Yes | No | Yes | Yes | No | NA | NA | Yes | NR | NA | No | Fair |
| Falck (2012) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | NR | NA | No | Good |
| Ford (2006) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | NA | Yes | NR | NA | No | Good |
| Forsyth (1999) | Yes | Yes | Yes | Yes | No | Yes | Yes | NA | Yes | NA | Yes | NR | NA | No | Good |
| Gana (2019) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | NA | Yes | NR | NA | No | Good |
| Gazibara (2018) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | NA | Yes | NR | NA | No | Good |
| Giacomuzzi (2006) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | NA | Yes | NR | NA | No | Good |
| Gjerde (2008) | Yes | Yes | Yes | Yes | No | Yes | NA | No | Yes | NA | Yes | NR | NA | No | Fair |
| Guimaeraes (2004) | Yes | Yes | Yes | Yes | No | Yes | NA | No | Yes | NA | No | NR | NA | No | Fair |
| Hagman (2007) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | No | No | Good |
| Hockenhull (2019) | Yes | Yes | Yes | Yes | Yes | Yes | NA | Yes | Yes | NA | Yes | NR | No | Yes | Good |
| Imran (2011) | Yes | Yes | Yes | Yes | No | Yes | NA | No | Yes | NA | Yes | NR | NA | No | Fair |
| Juan (2015) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NA | NA | Yes | Good |
| Kelly (2010) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NA | NA | Yes | Good |
| Khanal (2010) | Yes | Yes | Yes | Yes | No | Yes | NA | No | Yes | NA | Yes | NA | NA | No | Fair |
| Klare (2020) | Yes | Yes | Yes | Yes | No | Yes | NA | NA | Yes | NA | Yes | NR | NA | Yes | Good |
| Krebs (2005) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | NR | No | No | Good |
| Kurtz (2013) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | NR | Yes | No | Good |
| Kurtz (2016) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | NA | Yes | NR | NA | Yes | Good |
| Kushwaha (2019) | Yes | Yes | Yes | Yes | Yes | Yes | NA | NA | Yes | NA | Yes | NR | NA | No | Good |
| Levine (2009) | Yes | Yes | Yes | Yes | No | Yes | NA | No | Yes | NA | Yes | NR | NA | No | Fair |
| Li A (2019) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NA | NA | No | Good |
| Li B (2019) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | NR | Yes | No | Good |
| Lillsunde (1996) | Yes | No | NR | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | No | Fair |
| Liu (2005) | Yes | Yes | Yes | Yes | Yes | Yes | NA | Yes | Yes | NA | Yes | NR | NA | Yes | Good |
| Loiselle (1993) | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | NA | Yes | NR | NA | Yes | Good |
| Lott (2009) | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | NR | No | No | Good |
| Maddux (1986) | Yes | No | Yes | Yes | No | Yes | NA | No | Yes | NA | No | NR | No | No | Poor |
| Marin (2010) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | No | Good |
| Maust (2019) | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | Yes | Good |
| McCabe (2005) | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | No | Yes | Good |
| McCabe A (2007) | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | NA | Yes | No | Yes | Yes | Good |
| McCabe B (2007) | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | NA | Yes | No | No | Yes | Good |
| McCabe (2008) | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | Yes | Yes | Good |
| McCabe (2011) | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | NA | Yes | NR | Yes | No | Good |
| McCabe (2012) | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | Yes | No | Good |
| McCabe (2014) | Yes | Yes | Yes | No | No | NR | No | Yes | Yes | No | Yes | No | Yes | Yes | Good |
| McCabe (2019) | Yes | Yes | No | No | No | NR | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Good |
| McCaul (1988) | No | No | No | Yes | No | No | No | No | Yes | NA | No | No | No | No | Poor |
| McCauley (2010) | Yes | Yes | Yes | Yes | No | No | NA | No | Yes | No | Yes | No | No | No | Fair |
| Murphy (2018) | Yes | Yes | Yes | Yes | No | No | No | NA | No | No | NR | No | Yes | No | Poor |
| Murphy A (2014) | Yes | Yes | Yes | Yes | No | No | NA | No | Yes | No | Yes | No | Yes | No | Fair |
| Murphy B (2014) | Yes | Yes | Yes | No | No | No | NA | NA | Yes | No | Yes | No | Yes | No | Fair |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nawaz (2017)** | Yes | Yes | Yes | Yes | No | No | NR | No | No | No | Yes | No | Yes | No | **Fair** |
| **Nevadomsky (1982)** | Yes | No | Yes | No | No | No | NR | No | Yes | No | Yes | No | Yes | No | **Poor** |
| **Noffsinger (2019)** | Yes | No | Yes | No | No | No | Yes | Yes | Yes | No | Yes | No | Yes | No | **Fair** |
| **Noto (1997)** | Yes | Yes | Yes | Yes | No | No | NA | No | Yes | No | Yes | No | No | No | **Fair** |
| **Oesterle (2015)** | Yes | No | No | Yes | No | No | NA | Yes | Yes | No | No | No | No | No | **Poor** |
| **Olashore (2018)** | Yes | Yes | Yes | Yes | Yes | No | NR | No | Yes | No | Yes | No | Yes | Yes | **Good** |
| **Opaleye (2013)** | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | No | Yes | No | No | Yes | **Good** |
| **Opaleye (2014)** | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | Yes | **Good** |
| **Palamar (2019)** | Yes | No | NR | Yes | No | No | Yes | Yes | Yes | No | Yes | No | NR | No | **Fair** |
| **Paredes (2008)** | Yes | Yes | NR | Yes | No | No | NR | Yes | Yes | No | Yes | No | NR | No | **Fair** |
| **Parks (2020** | Yes | Yes | Yes | Yes | No | No | NR | No | Yes | No | Yes | No | Yes | Yes | **Good** |
| **Parry (2000)** | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | Yes | No | **Good** |
| **Paul (2018)** | Yes | Yes | NR | Yes | No | No | Yes | No | Yes | No | Yes | NA | NR | Yes | **Fair** |
| **Pedersen (2019)** | Yes | Yes | Yes | Yes | NA | NA | Yes | Yes | Yes | Yes | Yes | No | Yes | No | **Good** |
| **Philips (2014)** | Yes | Yes | Yes | Yes | No | No | NA | NA | Yes | No | Yes | No | No | No | **Fair** |
| **Pino (2017)** | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | Yes | **Good** |
| **Quintero (2006)** | Yes | Yes | Yes | Yes | No | No | NA | No | Yes | No | Yes | NR | Yes | No | **Fair** |
| **Rejent (1976)** | Yes | No | NR | NR | No | No | NA | Yes | Yes | No | Yes | NR | NR | No | **Poor** |
| **Rezahosseini (2014)** | Yes | Yes | No | Yes | No | No | NA | No | Yes | No | Yes | No | No | Yes | **Fair** |
| **Rickert (1999)** | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | Yes | Yes | **Good** |
| **Rickert (2000)** | Yes | Yes | Yes | Yes | No | No | No | No | Yes | No | Yes | No | Yes | Yes | **Good** |
| **Rigg (2014)** | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | NR | No | Yes | **Good** |
| **Rockett (2005)** | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | Yes | No | No | Yes | **Good** |
| **Sandi (2002)** | Yes | Yes | NR | Yes | No | No | NA | NA | Yes | NA | Yes | No | NR | No | **Fair** |
| **Schepis (2014)** | Yes | Yes | NR | Yes | No | No | Yes | Yes | Yes | No | Yes | No | NR | Yes | **Good** |
| **Schepis (2016)** | Yes | Yes | Yes | Yes | No | No | Yes | NA | Yes | No | Yes | No | Yes | Yes | **Good** |
| **Schepis B (2018)** | Yes | No | NR | Yes | No | No | Yes | No | Yes | No | Yes | NR | NR | Yes | **Fair** |
| **Shabbir (2018)** | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | Yes | No | **Good** |
| **Sharma (2015)** | Yes | Yes | NR | Yes | No | No | NR | Yes | Yes | No | Yes | No | NR | No | **Fair** |
| **Sheridan (2019)** | Yes | Yes | NR | No | No | No | Yes | No | No | No | Yes | No | NR | No | **Poor** |
| **Skurtveit (1995)** | Yes | No | NR | No | No | No | NA | NA | Yes | No | Yes | No | NR | No | **Poor** |
| **Solbergsdottir (2008)** | Yes | Yes | NR | Yes | No | Yes | NA | Yes | Yes | No | Yes | No | NR | No | **Fair** |
| **Spooner (2000)** | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Yes | No | Yes | No | Yes | Yes | **Good** |
| **Stone (2012)** | Yes | Yes | NR | No | No | No | NA | Yes | Yes | No | Yes | No | NR | Yes | **Fair** |
| **Tanidir (2015)** | Yes | Yes | NR | Yes | No | No | Yes | Yes | Yes | No | Yes | No | NR | No | **Fair** |
| **Tardelli (2019)** | Yes | Yes | Yes | Yes | No | No | No | No | No | No | Yes | No | No | Yes | **Fair** |
| **Tjäderborn (2016)** | Yes | No | NR | Yes | No | No | Yes | Yes | Yes | No | Yes | No | NR | Yes | **Fair** |
| **Viana (2012)** | Yes | Yes | NR | Yes | No | No | NR | No | Yes | No | Yes | No | NR | Yes | **Fair** |
| **Whiteside (2013)** | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | Yes | Yes | **Good** |
| **Wilson (1979)** | Yes | No | NR | Yes | No | Yes | NA | NA | Yes | NA | Yes | NR | NA | No | **Poor** |
| **Wu (2006)** | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | No | Yes | **Good** |
| **Yacoubian (2002)** | Yes | Yes | Yes | Yes | No | No | NA | Yes | Yes | No | Yes | No | No | Yes | **Good** |
| **Zullig (2012)** | Yes | Yes | Yes | Yes | No | Yes | NA | Yes | Yes | NA | Yes | NR | NA | Yes | **Good** |

*Note.* NA = not applicable; NR = not reported

* Question:

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?