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

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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.

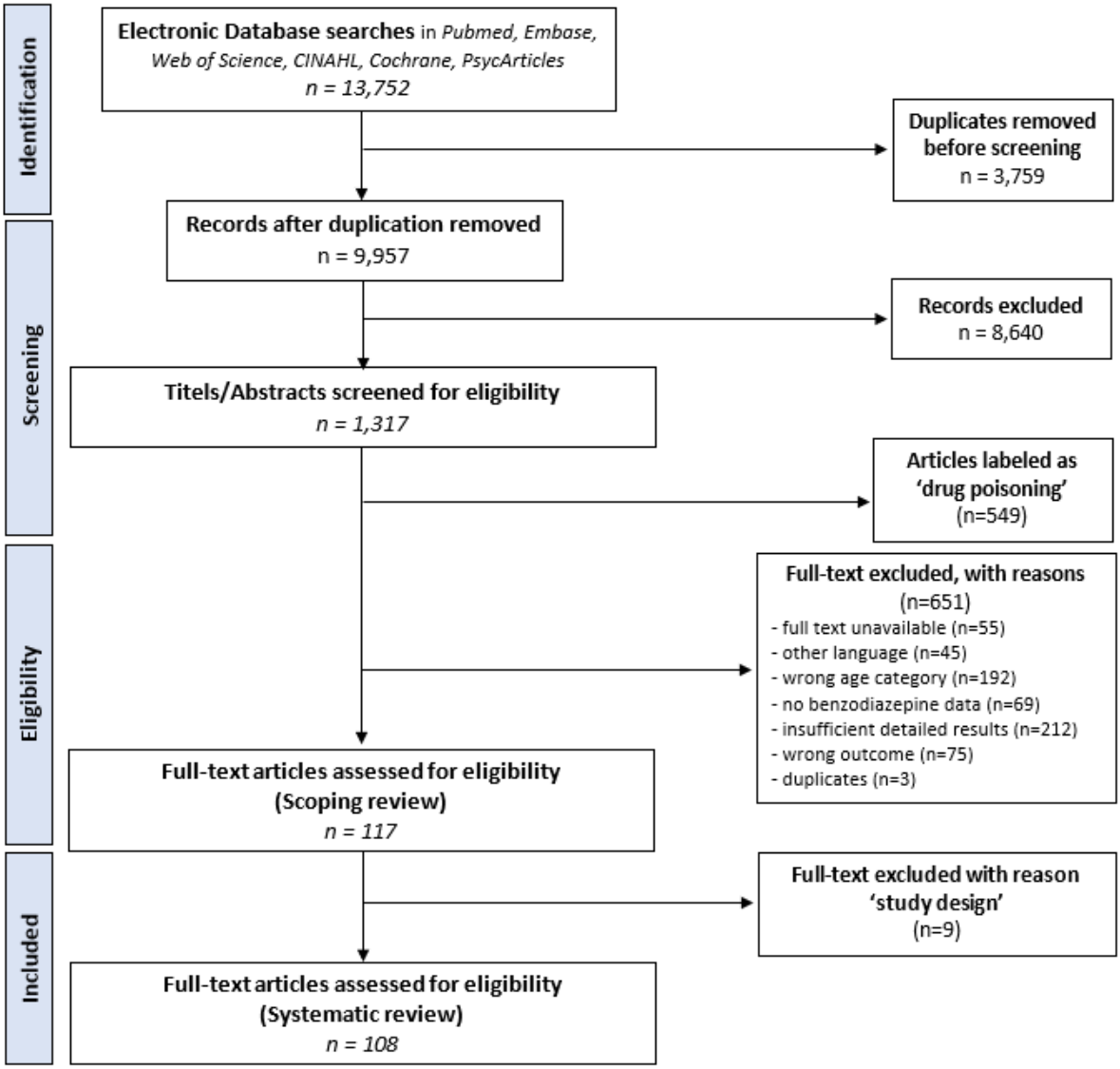
Results

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

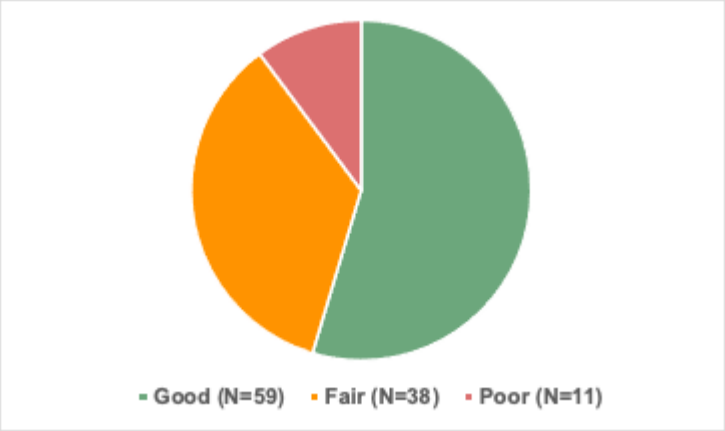


Quality assessment

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 2.4% NMU use	/	/	Sleeping medication (e.g., Ambien, Halcion, Restoril, temazepam, triazolam)

		only			
		2.4% NMU in combination with medical use 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 3% <1x/month use 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 3.0% NMU only	0.7% NMU in combination with medical use 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

De voorbije drie jaar hebben we samen hard gewerkt om deze thesis tot stand te laten komen. Naar mijn mening waren we een sterk team, waarbij er altijd ruimte was voor vragen of bedenkingen. Als we het niet eens waren, probeerden we dit constructief op te lossen en kwamen we altijd tot een consensus, waarin iedereen zich kon vinden. We spraken elkaar wekelijks om enerzijds inhoudelijke zaken af te toetsen, maar we vroegen ook altijd aan elkaar of iedereen het verdeelde werk rond kreeg tegen de afgesproken deadline. Het was niet altijd even gemakkelijk om de thesis te combineren met het werk in de huisartsenpraktijk. Hierbij konden we steeds op elkaar rekenen. We hielpen en motiveerden elkaar, zodat het werk fijn en haalbaar bleef. Ieders aandeel in deze thesis is dan ook even groot, daar we elkaars werk altijd nagelezen, verbeterd en aangepast hebben om tot een mooi geheel te komen.

We konden steeds beroep doen op onze co-promotor Kristien Coteur, die ons altijd van een uitgebreid antwoord voorzag op al onze grote en kleine vragen. Dit met een bemoedigende ondertoon, wat heel motiverend gewerkt heeft. Natuurlijk konden we ook steeds rekenen op de steun van onze promotor professor Cathy Matheï en nadien professor Marc Van Nuland, die ons richting en ondersteuning gaven waar nodig. Ik vond het erg fijn dat we op regelmatige basis afspraken, online of in het echt, zodat we meteen onze vragen konden stellen en verder konden werken met de verkregen feedback.

Aanvankelijk kozen we dit onderwerp, omdat we zelf vanuit de opleiding steeds hebben meegekregen dat we voorzichtig moeten zijn in het voorschrijven van z-drugs en benzodiazepines. Anderzijds wordt deze medicatie frequent voorgeschreven voor verschillende psyhische aandoeningen. Uit eigen ervaring merk ik dat patiënten regelmatig om deze medicatie vragen in het kader van slapeloosheid. Daarom vonden we het interessant om het misbruik hiervan in kaart te brengen, samen met mogelijke risicofactoren, screening methodes en de aanpak ervan. Het voorstel van professor Cathy Matheï om het misbruik te bekijken bij personen tot 25 jaar vonden we zeer nuttig, omdat deze leeftijdsgroep enerzijds aansluit bij onze eigen leefwereld en het anderzijds een kwetsbare leeftijdsgroep is, waarbij de cognitieve ontwikkeling volop aan de gang is en de schade ten gevolge van dit misbruik groot kan zijn.

Het werken aan de hand van een protocol, dat we samen met onze (co-)promotor hebben opgesteld, gaf een goede houvast. Ook de tijdslijn met de vooraf afgesproken deadlines hielp ons om goed op schema te blijven.

Bij het opstellen van onze initiële zoekstrategie vond ik het heel leerrijk om het gebruik en de eigenheid van de verschillende databases te leren kennen. Initieel waren we verrast door de omvang van de bestaande literatuur. Gaandeweg hebben we ons design aangepast van een scoping review naar een systematic review, waarbij er veel informatie verloren is gegaan. Dit was enerzijds spijtig, maar anderzijds vond ik het steeds heel fijn dat onze (co-)promotoren flexibel waren en mee naar oplossingen zochten, als de werkdruk te hoog lag.

Bij het gebruik van Rayyan QCRI voor de verdere screening heb ik veel bijgeleerd rond wetenschappelijk onderzoek. Hierbij verdeelden we steeds het werk en hielpen elkaar op technisch en inhoudelijk vlak. We werkten

altijd in duo's en vergeleken nadien de resultaten, waardoor er minder fouten gemaakt konden worden. Nadien bij het charten van de data hebben we vooral gewerkt met Excell en ook dit vond ik een hele handige manier van werken. Dit is zeker iets dat ik ga meenemen bij het schrijven van een volgend wetenschappelijk werk.

Op inhoudelijk vlak neem ik vooral mee dat het misbruik van z-drugs en benzodiazepines meer voorkomt in deze jongere leeftijdsgroepen, dan we initieel gedacht hadden. Dit betekent dat het enerzijds een problematiek is, waar we als (huis)arts rekening mee moeten houden, en anderzijds dat er nog meer onderzoek vereist is. Persoonlijk zou ik het ook nuttig vinden om te kijken wat de motivatiebronnen zijn tot misbruik van deze medicatie in deze leeftijdsgroep.

Ik vind het spijtig dat de studies nooit uitgevoerd zijn in de eerste lijn, wat opnieuw heel interessant kan zijn voor verder onderzoek. Toch heb ik veel geleerd over de mogelijke risicofactoren voor het misbruik van z-drugs en benzodiazepines, wat wel nuttig kan zijn in de huisartsenpraktijk.

Achteraf gezien was het een heel leerrijk en boeiend proces met hier en daar wat moeilijkheden, maar vooral met veel kleine successen en uiteindelijk een mooi resultaat, waar we trots op zijn.

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Appendix A

Search Strategy

Pubmed	**Concept 1:** ("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]) **Concept 2:** ("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]) **Concept 3:** ("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:** (‘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) **Concept 2:** (‘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) **Concept 3:** (‘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:** (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") **Concept 2:** (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") **Concept 3:** (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:** [mh "Benzodiazepines"] OR [mh "Zolpidem"] OR [mh "Eszopiclone"] OR (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 **Concept 2:** [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"] OR (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 **Concept 3:** [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"] OR (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:** 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”) **Concept 2:** 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”) **Concept 3:** 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:** 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”) **Concept 2:** 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”) **Concept 3:** 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)?