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Advise use of psychotropic drugs during pregnancy in the Netherlands between 2000-2021

BACHELOR PROJECT (WBFA902-14.2020-2021.2A)

Michelle van der Ploeg (S3304523)
SUPERVISION: R. ROBIYANTO M. PHARMSC, DR. S. BORGSTEEDE, PROF. DR. E.P. VAN PUIJENBROEK |

Abstract

A recent study shows that the prevalence rate of psychological and psychiatric disorders during pregnancy is almost 20%.[1] These conditions can be treated with psychotropic drugs, categorized in ATC classes N05, N06 and N07. These classes concern the psycholeptics (N05), psychoanaleptics (N06) and other various nervous system (NS) targeting drugs (N07). These psychotropic drugs alter neurotransmitter levels in the nervous system and hence treat the symptoms of psychological disorders. However, the pharmacokinetic and -dynamic effects of psychotropic drugs in pregnant women remain unknown during the clinical phases, as due to ethical issues pregnant women are excluded in the drug development phases. Only after approval of the drug, its effects are monitored by means of spontaneous reporting systems, for example by the Dutch pharmacovigilance centre Lareb, and by dedicated pregnancy registries, for example by the Dutch pREGnant register.[2] The collected data can be used to create and adjust safety classification systems for advice regarding pharmacological treatment with psychotropic drugs during pregnancy. These classification systems have been subject to adjustments over time. It is possible that the view on the safety of a specific drug has altered, or it is possible that it is caused by a change in the classification itself. However, it is not known when a drug classification has changed, how the classification has changed and why the classification system has changed. Whilst exactly this information is crucial in understanding the teratogenicity of certain psychotropic drugs. Therefore, this project provides an overview of the advice for psychotropic drugs during pregnancy over time and identifies the underlying reasons on which the change in safety classification of psychotropic drugs during pregnancy is based in the Netherlands between 2000-2021. In total, nineteen safety classification changes for psychotropic drugs have been observed. The number of changes for the psycholeptics was significantly lower compared to the number of changes in the other psychotropics. The number of changes in the psychoanaleptics was significantly higher than the number of changes in the other psychotropics. The number of changes for class N07 was not significantly different than the number for the other psychotropics. For all ATC classes, no significant difference in the number of changes in the first decade (2000-2010) compared to second decade (2010-2021) was found. In addition, not a single nature of change had a significant impact on the total number of changes and was thus not of great importance. It was the first time such a study had been conducted. For future research, it might be interesting to look into the effect of a change in advice regarding the psychotropic drug utilization during pregnancy.

Table of Contents

Introduction

More and more individuals are diagnosed with mental health problems. This results in the fact that mental health problems are a major contributor to the total burden of disease worldwide.[3] Into the bargain, these mental health problems are among the comorbidities during pregnancy, with prevalence ranging between 10-20% for pregnant women.[4,5]

Pharmacological treatment of mental health problems may consist of therapeutic intervention with psychotropic drugs (ATC classification starting with: N05, N06 and N07).
These classes concern drugs targeting the nervous system; for example, psycholeptics, psychoanaleptics, anti-addictives and antivertigo drugs. These drugs affect the neurotransmitter levels in the central nervous systems and hence treat the symptoms of the various psychological disorders. For example, citalopram is a selective serotonin reuptake inhibitor (SSRI) used for the treatment of depression. Citalopram increases the serotonergic neurotransmission by preventing serotonin uptake in the presynaps.[6]
However, the information on teratogenicity of psychotropic drug use during pregnancy is missing as during drug development, pregnant women are excluded, which increases the uncertainty in respect to the safety of use of psychotropic drugs during the pregnancy. On the other hand, there are also risks when pregnant women are not treated for their psychiatric disorders, which may even be more harmful than the treatment with psychotropic drugs.[7,8]

To guide healthcare professionals in the decision making whether to treat or not to treat, safety classifications can be consulted. Some examples of these classifications in the Netherlands are the Teratologie Informatie Service (TIS) and Health Base Foundation. Besides national systems, also international classification systems are available. For example, the Australian Drug Evaluation Committee (ADEC), Swedish Catalogue of Approved Drugs (FASS) and the American Food & Drug Administration (FDA) maintain safety classification systems.

These various classification systems have been adjusted over time via two mechanisms, one mechanism being the adjustment of the safety of a drug due to a gain in knowledge for example and the other mechanism being the adjustment of the categories in the system itself. Nonetheless, information about the date of an adjustment, the reasons behind an adjustment and how the classification is adjusted, is lacking. Therefore, the general aim of this study is to provide an overview of the changes in risk classification for the use of psychotropic drugs (ATC codes N05, N06 and N07) during pregnancy in the Netherlands between 2000–2021. The secondary aims are to identify the underlying reasons for the observed changes in risk classification for psychotropic drugs (ATC codes N05, N06 and N07) during pregnancy and to determine the existence of differences in the observed number of risk classification changes between the ATC codes, between the first and second decade and between the nature of change.

Psychotropic drugs

The ATC code N05 has been assigned to the psycholeptics. This group is divided into three therapeutic subgroups: antipsychotics, anxiolytics, hypnotics and sedatives.
The ATC code N06 belongs to the psychoanaleptics. The subdivision of this class is as followed: antidepressants, psychostimulants, combination therapy of N05/N06 and antidementia drugs.
The ATC code N07 is assigned to other drugs targeting the nervous system, for example parasympathomimetics, drugs for addictive disorders and antivertigo drugs.[9] For a clear overview, *Table 1* can be consulted.

Table 1: ATC classification 2021 from World Health Organization of N05, N06 and N07.[9]

ATC N05	
N05A	antipsychotics
N05B	anxiolytics
N05C	hypnotics/sedatives

ATC N06	
N06A	antidepressants
N06B	psychostimulants
N06C	combi. N05/N06
N06D	antidementia

ATC N07	
N07A	parasympathomimetics
N07B	anti-addictive
N07C	antivertigo

Drugs assigned to these classes are of importance for the use advise of psychotropic drugs during pregnancy in the Netherlands for the last two decades.

Risk of untreated psychological disorders during pregnancy

The mode of action of psychotropic drugs is to alter the neurotransmitter levels in the brain and hence influence the symptoms of the psychiatric disorder. The ease of use and safety of psychotropic drug use always effects two individuals; the pregnant women and the unborn child.[10] Both ceasing treatment and continuing treatment of the psychiatric disorder comes with risks. It might be the case that the risk of not treating the disorder in pregnant women outweigh the risk of the continuation of treatment, from which the potential for teratogenicity is not fully comprehended.

It is for example known that for untreated sleep disorders, a higher prevalence of prenatal depression, gestational diabetes, preeclampsia, increased length of labour, increased risk for caesarean labour and preterm birth are found.[9] Additionally, untreated anxiety has negative effects both pre- and postnatal although the exact reasons are not understood yet.[11,12,13,14] Furthermore, untreated bipolar disorder and schizophrenia showed an increased risk at the reoccurrence of mood swings during pregnany.[15] Also, untreated depression led to an increase in prevalence of premature delivery, reduced initiation of breastfeeding, low birth weights, hyperactivity and irregular heartbeat and fetal growth restrictions.[7,8] These effects are harmful to the new-born but also the pregnant women are at risk. Untreated depression may lead to feelings as sadness and tiredness, making it hard for the women to take proper care of themselves, which can lead to smoking, drinking and substance abuse during pregnancy.[16] Arresting treatment for attention deficit hyperactivity disorder (ADHD) also comes with interindividual risks; Some women experience no problems, whereas some do. Some effects of untreated ADHD are risks of being involved in vehicle accidents and functioning problems. The effects on the fetal development are hardly studied and future research should be conducted.[17]

All in all, terminating the treatment of psychological disorders on some occasions is not an option. The risks and benefits of (interrupting) pharmacological treatment should be considered on an individual level by the health care professionals.[11,17] And to guide health care professionals in which drug to use, various safety classification systems can be consulted.

Objectives

The general aim of this study is to provide an overview of the changes in risk classification for the use of psychotropic drugs (ATC codes N05, N06 and N07) during pregnancy in the Netherlands between 2000–2021.

The general aim encompasses a number of secondary aims:

a) To identify the underlying reasons for the observed changes in risk classification for psychotropic drugs (ATC codes N05, N06 and N07) use during pregnancy.
b) To study differences in the observed number of classification changes within a specific ATC class versus the other psychotropic drugs
c) To study differences in the observed number of safety classification changes between the first and second decade.
d) To study differences in the nature of the safety classification change within an ATC code.

National and international safety classification systems for psychotropic drug use during pregnancy

In order to study the change in advice with respect to psychotropic drug use during pregnancy, first the various national and international safety classification systems have to be understood.

Safety classifications in the Netherlands

The Teratologie Informatie Service (TIS; www.lareb.nl/tis-knowlegde) was part of the National Institute for Public Health and the Environment (RIVM) in the Netherlands until 2011. Nowadays, it is part of the Dutch national pharmacovigilance centre Lareb. TIS provides an annual report regarding the information from Lareb in one of the 'medicatiemonitoring' textbooks in the Netherlands. This textbook is implemented in the Pharmacy and Physician information systems.[18]
The information is gathered and updated in various manners. The Lareb Intensive Monitoring (LIM) pro-actively gathers information via patients filling in surveys about their experiences with medicines and vaccines. In addition, patients are able to report experienced side effects, upon which signals are passed on to the College ter Beoordeling van Geneesmiddelen and EMA.[19]

Over time, TIS has been using different classification systems. The latest safety classification system consists of the tags: *most safe, probably safe, possible risk, risk at birth defect* and *unknown risk.* The safety classification system beforehand used the tags: *maintain, limit, weigh up* and *stop.* The new classification system gives more information about the risks for the fetal development compared to the before used system.[20]
TIS has changed its name into 'Moeders van Morgen', it maintains the pregnancy registry pREGnant and hence gives advice about the use of psychotropic drug during pregnancy and lactation.[21]

In addition, Health Base Foundation, which is an independent centre of expertise for drug information and medication monitoring, provides information that is based on and maintained by TIS and can be consulted by health care professionals. Health Base was founded in 1990 by pharmacists to develop information files for the pharmacy information system (AIS) *Pharmacom* from *Pharmapartners*.
Health Base also provides the 'Commentaren Medicatiebewaking' textbook with pharmacovigilance advise. This textbook consists of guidelines about pharmacological treatment in general, and special chapters on the use of drugs during pregnancy and lactation. Information for the latter chapters is maintained by TIS.[22] The textbook has a classification system for pregnancy and lactation related drug use, based on the Australian, Swedish and TIS system.

Farmacotherapeutisch Kompas (FK, www.farmacotherapeutischkompas.nl) also can be consulted. The FK has a database comprised of drugs that are approved by the College ter Beoordeling van Geneesmiddelen (CBG) and/or European Medicines Agency (EMA).[23] The FK does not have its own classification system; it tells whether a compound is teratogenic and/or has pharmacological effects. This information is based on the formal product information and the advice provided by TIS. Besides, it gives advice regarding the treatment continuation and what is best to do during both pregnancy and lactation. The FK also refers to the registry Lareb if more information is wanted.[24]
On top of these well-known sources, also 'apotheek.nl', 'Landelijk Kenniscentrum Psychiatrie en Zwangerschap' and 'Richtlijnendatabase' can be consulted.[25,26,27,28] These units give advice about various drugs, still do not maintain a safety risk classification.

International safety classifications

The Australian Drug Evaluation Committee (ADEC) was founded as an independent committee in 1963 after the thalidomide incident. The function of ADEC was to make medical and scientific evaluations on therapeutic substances. With this knowledge, the ADEC advises on the safety of drugs

and guides the decisions made by the Therapeutic Goods Administration (TGA) of the Australian Government, department of health.[29]

In 2010, ADEC was replaced by the Advisory Committee on Prescription Medicines (ACPM), which was replaced again by the Advisory Committee on Medicines (ACM) in 2017. The function of the committee however never changed; classify legal drugs on the safety of use during pregnancy and provide independent medical and scientific advice to the TGA.[30]

The ACPM and ACM have used the same safety classification (A, B, C, D, X) system as the ADEC.[31,32]

The Swedish safety classification system, Farmaceutiska Spesialiteter i Sverige (FASS), is founded by Läkemedelsindustriföreningen (LIF) in collusion with the Medicinal Products Agency (MPA) and additional help in 1966. LIF is the research-based pharmaceutical industry in Sweden. The FASS shares information and updates about medicines. The pregnancy and breastfeeding classification information is shared by the Uppsala University.[33]
The Swedish safety classification (A, B, C, D) has not went through adjustments.

The American Food and Drug Administration (FDA) has been operational since 1848. Back then, its main function was to analyse the safety of agricultural products. In 1962, the Kefauver-Harris Drug Amendments were passed to ensure drug efficacy and safety, after the thalidomide incident.[51;34] The FDA has been using two classifications over the years. The first classification, in use until 2015, consisted of a letter-code (A, B, C, D, X) in order to classify drugs. This system has been exchanged for the Pregnancy and Lactation Labelling Rule (PLLR) in 2015.[34,35]

On top of these, also the World Health Organization and Evidence-Based Medicine can be consulted for information about psychotropic treatment during pregnancy. These however only provide information and do not maintain an own classification system.[36]

Methods

To get an overview of the various pharmacovigilance centres and independent foundations, internet research in combination with literature research was done. The inclusion criteria for internet sources were as followed: detailed background information about the author and/or organization responsible for the content of the site, the site is well-maintained and is updated regularly, a clear structure and well-formulated sentences without spelling mistakes, and it should contain links to sites from other reliable sources.

To get an overview about how drugs were classified the last two decades, the *Commentaren Medicatiebewaking* (CM) textbooks published during the last two decades were perused. The CM has been using three different safety classification systems during the past two decades. For the classes in each safety classification systems, letter codes as abbreviations were used to create a clear overview.

The first system, in use until CM edition 2008/2009, uses a classification system with the categories A, B (1/2/3), C and D. Safety class A consisted of drugs which did show to be hazardous to pregnant women and are thus safe to use during pregnancy. Safety class B consisted of drugs from which insufficient knowledge was available about safety of use during pregnancy. Safety class C consisted of drugs which showed to have pharmacological effects in pregnant women but did not lead to malformations in the new-borns. Safety class D consisted of drugs from which hazardous effects have been observed in pregnant women. This classification was used directly in the overview:

- *A* → A
- *B (1/2/3)* → B (1/2/3)
- *C* → C
- *D* → D

To give an example: haloperidol is classified to be in *class C* in edition 2000/2001, therefore in the overview the letter C was depicted.

The system in use in CM edition 2008/2009 until edition 2019/2020, used a more descriptive safety classification. The following letter codes per class were used in the overview:

- *Broad experience; can be used*. → R
- *Pharmacological effect; monitor during use.* → F
- *Pharmacological effect; do not use (temporarily).* → FN
- *Teratogenic effect; monitor during use.* → T
- *Teratogenic effect; do not use (temporarily).* → TN
- *Insufficient experience; unknown risks.* → O

To give an example: haloperidol is classified as '*pharmacological effect; monitor during use'* in edition 2009/2010, therefore in the overview the letter T was depicted.

The classification system in use from edition 2020/2021 of 'Commentaren Medicatiebewaking' also uses the descriptive classification. To establish a clear overview, the safety classification was linked to a letter code. The following code was used:

- *Most safe.* → MV
- *Probably safe.* → WV
- *Most safe/probably safe under certain conditions.* → WO
- *Unknown risks.* → O
- *Potential risks.* → MR
- *Risks at birth defects.* → RA

To give an example: haloperidol is classified as '*probably safe in the 1st and 2nd trimester* and has *potential risks in the 3rd trimester* in 2020/2021, therefore in the overview WV (1e/2e)/MR (3e) was depicted. With the overview, the changes per year per drug were visualized.

However, a methodological problem arose; the classification system of the CM itself has changed three times between 2000-2021. This results in the fact that all drugs were changed in classification due to the change in the system itself. It was important, when the safety classification of drugs was studied, to check whether a drug has changed its safety classification due to a change in the system itself, or by means of information gain about the safety of a drug.
This problem was solved by aligning the safety classifications used over the last two decades. For example, *B* (System I: till 07/08), *insufficient experience; unknown risks* (System II: from 08/09-19/20) and *unknown risks* (System III: from 20/21 on) were aligned as they presented similar subject matters. Namely, the core was that insufficient knowledge about the safety of this drug was available when the drug was used during pregnancy. This similar subject-matter allowed alignment of the safety classification. This was done in the same matter for the other classes and resulted in the alignment table, which can be found in *Table 2.*

Table 2: Alignment of the safety classifications from System I, II, and III from Commentaren Medicatiebewaking from Health Base.

System I (till 07/08)	System II (from 08/09 till 19/20)	System III (from 20/21 on)
A	Broad experience; can be used. (R)	Most safe. (MV)
A or B (1/2/3)		Probably safe. (WV)
		Most safe/ probably safe under certain conditions. (WO)
C	Pharmacological effect; monitor during use. (F)	Potential risks. (MR)
	Pharmacological effect; do not use (temporarily). (FN)	
D	Teratogenic effect; monitor during use. (T)	Risks at birth defects. (RA)
	Teratogenic effect; do not use (temporarily). (TN)	
B	Insufficient experience: risk is unknown. (O)	Unknown risks. (O)

If a drug had changed its safety classification outside the alignment, it was placed in the overview. After the overview was created, it was clear to see when a drug had changed and how a drug had changed from safety classification. This allowed to create an overview of the changes per year. The identification of the underlying reasons of these changes was done by perusing the Commentaren Medicatiebewaking textbook and by literary research. To create a clear overview of the motivation of the safety class adjustment, a categorization of motivation behind the changes was created. The categories were as followed after personal communication:

1. New available studies focused on the safety of a drug during pregnancy
2. Increased experience; increased number of drug exposure during pregnancy (>1000 case reports)
3. Labelling change or EMA change
4. Old, extensively used drug without studies focused on drug safety during pregnancy or without known number of drug exposure during pregnancy.
5. Miscellaneous

Ad 1: The safety classification of a drug can be adjusted due to an information gain, by for example the publication of a study which focusses on the safety of the drug use during pregnancy. The information gain about the safety of a drug can go into different directions, either the study

associates the use of the drug with an increased risk/prevalence at pharmacological effects or malformations. Another possible outcome is the opposite of the previous mentioned findings: the use of a drug is not associated with an increased risk/prevalence at pharmacological effects or malformations. In addition, when published studies are unambiguous the drug might also be moved to another safety classification.

Ad 2: Health Base uses, based on the *guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling* published by the EMA, specific number of exposures as borders for classifications. When, within at least 1000 collected drug exposed pregnancies, no increased prevalence of pharmacological effects or malformations are observed, the conclusion can be drawn that the use of the drug during pregnancy does not result in a 2-fold or more increase of the overall incidence of pharmacological effects or malformations. Hence, when experience is gained and the border of 1000 exposed pregnant women is reached without side effects, the drug may be moved to another safety classification.

Ad 3: The manufacturer of a drug has the capability to construct the label. When the manufacturer itself decides to state an utterance, it might be the case the classification of a drug has been adjusted.

Ad 4: Old, extensively used medicine were placed in the safe to use during pregnancy safety category often. The idea behind it is simple: the drug has been used for many decades without any major side effect signalling. However, from these old drugs it might be the case that literature is insufficient or lacking. Thus, when health care professionals asked questions as to why the drug was classified as safe to use during pregnancy substantiated evidence was lacking. This came with some unease and led to the decision to reclassify these specific drugs into the safety category consisting of drugs from which the risks are not known. It might also be possible that the number of pregnancy exposures is not tracked accordingly, hence the border of at least 1000 pregnancy exposures is not exceeded, causing the reclassification of the drug.

Ad 5: Reasons behind classification changes, which does not compromise with the already mentioned reasons, are situated in this category. An example is the classification change of hydroxyzine in *Commentaren Medicatiebewaking* edition 2005-2005. The motivation behind the change was that the drug was also used for other indications.

After was mapped when drugs had changed the safety classification, how the drugs were changed and what the motivation behind the change was, it was determined whether there was existence of statistically significant differences within and between the psycholeptics (N05), psychoanaleptics (N06) and other nervous system drugs (N07).

At first, the differences in the observed number of classification changes within a specific ATC class versus the other psychotropic drugs were studied. This was done by comparing the number of changed safety classifications of drugs with the number of drugs that do not have a changed safety classification. This provides information about the fact that the specific ATC code has been exposed to a significant number of changes, or that the advice within an ATC code has not been changed over time. A Chi-2 was used to test for possible differences and the Crude Odds ratio was used to easily see which ATC code had the lower amount of data.

Then, the differences in the observed number of safety classification changes between the first and second decade were studied within a specific ATC class versus the other psychotropic drugs. This was studied by comparing the number of changed safety classifications of drugs in the first decade (2000-2010) to the number of changed safety classifications of drugs in the second decade (2010-2020). A Chi-2 or exact Fisher test was used to test for possible differences and the Crude Odds ratio was used to easily see which ATC code had the lower amount of data and the Crude Odds ratio was used to easily see which ATC code had the lower amount of data.

At least, the differences in the nature of the safety classification change within an ATC code were studied. This was studied by comparing the number of changes within a specific nature to the total number of changes of the ATC codes. This provided information whether a specific nature of change had a significant impact on the total number of changes, and whether that specific nature of change was thus of great importance. A Chi-2 or exact Fisher test was used to test for possible differences and the Crude Odds ratio was used to easily see which nature of change had the lower amount of data.

The statistical analyses were done using SPSS statistics edition 25 software. The following claims were used: H_0 = No significant difference is found between the data. H_A = A significant difference is found between the data. If $p>0.05$, H_0 should be not rejected. If $p<0.05$, H_0 should be rejected. The α was 0.05.

Results

Various safety classifications used as guidelines for treatment of psychological disorders during pregnancy

Various pharmacovigilance centres are available to be consult about advice of psychotropic treatment during pregnancy and lactation. For an overview of the safety classification systems from CM published by Health Base, in the Netherlands during 2000-2010, *Table 3* can be consulted. For an overview of the international safety classification systems of Australia, Sweden and America between 2000-2010, *Table 4* can be consulted.
For an overview of the safety classification systems from CM published by Health Base, in the Netherlands during 2010-2021, *Table 5* can be consulted. For an overview of the international safety classification systems of Australia, Sweden and America between 2010-2021, *Table 6* can be consulted.

Safety classification systems during the first decade (2000-2010)

The safety classification systems in use by Health Base between 2000-2010 can be seen in *Table 3*. International safety classification systems of Australia, Sweden and America can be seen in *Table 4*.

Safety classification systems during the second decade (2010-2021)

The safety classification systems in use by Health Base between 2010-2021 can be seen in *Table 5*. International safety classification systems of Australia, Sweden and America can be seen in *Table 6*.

Risk classification for psychotropic drugs which are frequently prescribed during pregnancy in the Netherlands over the past 20 years

An overview of the risk classification for psychotropic drugs which are frequently prescribed during pregnancy in the Netherlands over the past two decades, can be found in *Table 7.* The classification of the drugs in the CM can be found in Appendix 2.

The adjustments of safety classifications of drugs used during pregnancy based on Commentaren Medicatiebewaking from Health Base between 2000-2021

An overview of the year of adjustments in safety classification and the reasons behind the adjustments adapted from Commentaren Medicatiebewaking can be seen in *Table 8*.

Table 3: Safety classification systems of Health Base in the Netherlands between 2000-2010.

Health Base Foundation classification system 2000-2010

System I (until 08/09)		*System II (08/09-19/20)*	
Category	Criteria/Definition	Category	Criteria/Definition
A	In studies involving pregnant women, no hazardous effects were observed (safe).	**Broad experience; can be used. (R)**	Medications used in studies and in practice of which no increased prevalence in deviations or indirect harmful effects were observed.
C	Pharmacological effects seen in foetus/neonate, though no malformations. Consider the use of medication, and preferably choose a safer alternative medication.	**Pharmacological effect; monitor during use. (F)**	Medications which are known or suspected to be causing effects to the embryonic development, without leading to malformations. Control during use.
		Pharmacological effect; do not use (temporarily). (FN)	Medications which are known or suspected to be causing effects to the embryonic development, without leading to malformations. Do not use (temporarily).
D	Hazardous effects observed (or likely); increased change of permanent damage to embryo/foetus. Use during pregnancy is not safe! Choose a safer option, if possible.	**Teratogenic effect; monitor during use. (T)**	Medications which are known or suspected to be leading to an increased prevalence of fetal disorders or other permanent damage. Consider the use of medication. Monitor during use on unwanted effects.
		Teratogenic effect; do not use (temporarily). (TN)	Medications which are known or suspected to be leading to an increased prevalence of fetal disorders or other permanent damage. Do not use medication; look for an alternative.
B	Insufficient research available from use in pregnant women. **B1**: No harmful effects observed in animal studies. **B2**: Possible effects insufficiently investigated in animals. **B3**: Hazardous effects observed in animal studies. Consider the use of medication, and preferably choose an alternative medication that has been investigated to a larger extent (category A or C).	**Insufficient experience; unknown risks. (O)**	Medications of which insufficient data on the effect in humans is available to determine the safety for the course of the pregnancy, the unborn child or new-born. Consider the use of medication.

Health Base adapted from 'Commentaren Medicatiebewaking' Editions 1999/2000-2009/2010.

Table 4: International safety classification systems of Australia, Sweden and America between 2000-2010.

International safety classification systems used between 2000-2010

Australian Drug Evaluation Committee (ADEC)		*Swedish Catalogue of Approved Drugs (FASS)*		*American Food & Drug Administration (FDA)*	
Category	Criteria/Definition	Category	Criteria/Definition	Category	Criteria/Definition
A	Drugs taken by a large number of pregnant women without an increase in prevalence of malformations or other direct/indirect harmful effects seen.	**A**	Drug assumed to be used by a large number of pregnant women did not result in any identified disturbances in the reproductive process. This category holds drug used for many years and drugs from retrospective studies showing no harmful effects.	**A**	Controlled clinical trials do not show an increased prevalence of risks to the foetus in the first trimester. And the possibility of harmful effects appears remote.
B	Drugs taken by a limited number of pregnant women. Experience is limited. **B1**: no harmful effects observed in animal studies. **B2**: possible effects insufficiently investigated in animals. **B3**: hazardous effects observed in animal studies.	**B**	Drugs taken by a limited number of pregnant women which did not result in identified disturbances. **B1**: reproduction animal studies did not show harmful effects. **B2**: reproduction animal studies are inadequate or lacking, but data did not show harmful effects. **B3**: reproduction animal studies show increased prevalence of harmful effects.	**B**	Animal studies showed or did not show fetal risks, but there are no confirmed controlled studies in pregnant women.
C	Drugs which, due to their pharmacological profile, have caused or are suspected to cause harmful effect without causing malformations.	**C**	Drugs that have caused, or are suspected to cause, due to their pharmacological profile, disturbances in the reproductive process without being directly teratogenic.	**C**	Either studies in animals showed adverse effects, but there are no controlled studies in pregnant women. Or studies in both animals and pregnant women are not available.
D	Drugs which have caused an increased incidence of human fetal malformations or irreversible damage.	**D**	Drugs which have caused an increased prevalence of fetal malformations or other permanent damage in humans. These drugs have teratogenic effects.	**D**	Positive evidence of harmful effects is found, but the use of drugs in pregnant women is acceptable despite the risk.
X	Drugs which have such a high risk of causing damage to the foetus that these drugs should not be used.			**X**	Studies in animals or humans have demonstrated an increase in prevalence of fetal abnormalities. The drug is contraindicated.

ADEC adapted from Addis et al.;[37] Fass adapted from Olesen et al and Addis et al.[37,38] FDA adapted from Frederiks et al and Addis et al.[36,39]

Table 5: Safety classification systems of Health Base in the Netherlands between 2010-2021.

Health Base Foundation safety classification 2010-2021

System II (08/09-19/20)		*System III (from 2020/2021 on)*	
Category	Criteria/Definition	Category	Criteria/Definition
Broad experience can be used. ®	Medications used in studies and in practice of which no increased prevalence in deviations or indirect harmful effects were observed.	**Most safe. (MV)**	Medication, within its drug class, is the safest option to use during pregnancy. No increased risk of birth defects or other disadvantageous effects on the pregnancy itself are found, in research or in practice.
Pharmacological effect; monitor during use. (F)	Medications which are known or suspected to be causing effects to the embryonic development, without leading to malformations. Control during use.	**Probably safe (WV)**	Medication can be used during pregnancy. Though, if available, use a medication from the category 'most safe'.
Pharmacological effect; do not use (temporarily). (FN)	Medications which are known or suspected to be causing effects to the embryonic development, without leading to malformations. Do not use (temporarily).	**Most safe/probably safe under certain conditions. (WO)**	Medication is (likely) to be used safely during pregnancy. Though, alternative medicines that belong to the category 'most safe', are preferred.
Teratogenic effect; monitor during use. (T)	Medications which are known or suspected to be leading to an increased prevalence of fetal disorders or other permanent damage. Consider the use of medication. Monitor during use on unwanted effects.	**Potential risk. (MR)**	Medication may have disadvantageous effects on both the pregnancy and the unborn child. Carefully weigh the potential adverse effects against the benefits in the mother's interest. Consider a safer alternative or monitor heavily.
Teratogenic effect; do not use (temporarily). (TN)	Medications which are known or suspected to be leading to an increased prevalence of fetal disorders or other permanent damage. Do not use medication; look for an alternative.	**Risk of birth defects. (RA)**	Medication has increased risk of causing birth defects or other permanent damage.
Insufficient experience; unknown risks. (O)	Medications of which insufficient data on the effect in humans is available to determine the safety for the course of the pregnancy, the unborn child or new-born. Consider the use of medication.	**Unknown risk. (O)**	Lack of or insufficient information about the use of medication during pregnancy. Impossible to comment on safety. Preferably choose alternative medicine of which more safety data is known.

Health Base adapted from the 'Commentaren Medicatiebewaking' editions 2008/2009-2020/2021.

Table 6: International safety classification systems of Australia, Sweden and America between 2010-2021

Various international safety classification systems used between 2010-2021

Australian Drug Evaluation Committee (ADEC)		*Swedish Catalogue of Approved Drugs (FASS)*		*American Food & Drug Administration (FDA) (from 2015 on)*	
Class	Criteria/Definition	Class	Criteria/Definition	PLLR	Content
A	Drugs taken by a large number of pregnant women without an increase in prevalence of malformations or other direct/indirect harmful effects seen.	**A**	Drug assumed to be used by a large number of pregnant women did not result in any identified disturbances in the reproductive process. This category holds drug used for many years and drugs from retrospective studies showing no harmful effects.	**Summary**	Description of the risks of a drug based on relevant human data, animal data and the drugs' pharmacology.
B	Drugs taken by a limited number of pregnant women. Experience is limited. **B1**: no harmful effects observed in animal studies. **B2**: possible effects insufficiently investigated in animals. **B3**: hazardous effects observed in animal studies.	**B**	Drugs taken by a limited number of pregnant women which did not result in identified disturbances. **B1**: reproduction animal studies did not show harmful effects. **B2**: reproduction animal studies are inadequate or lacking, but data did not show harmful effects. **B3**: reproduction animal studies show increased prevalence of harmful effects.	**Clinical considerations**	Provides further information for the risk-benefit counselling: - Disease associated maternal and/or embryo/fetal risk - Dose adjustment during pregnancy and postpartum period - Maternal adverse reactions - Fetal/neonatal adverse reaction - Labour or delivery
C	Drugs which, due to their pharmacological profile, have caused or are suspected to cause harmful effect without causing malformations.	**C**	Drugs that have caused, or are suspected to cause, due to their pharmacological profile, disturbances in the reproductive process without being directly teratogenic.		
D	Drugs which have caused an increased incidence of human fetal malformations or irreversible damage.	**D**	Drugs which have caused an increased prevalence of fetal malformations or other permanent damage in humans. These drugs have teratogenic effects.	**Data**	Describes both the animal and human data which provide the information for the risk summary and clinical considerations.
X	Drugs which have such a high risk of causing damage to the foetus that these drugs should not be used.				

ADEC adapted from Addis et al.[37,40,41] FASS adapted from Addis et al.[37] FDA adapted from FDA.[39]

Table 7: Overview safety classification frequently prescribed psychotropic drugs during 1999-2021 adapted from Health Base's 'Commentaren Medicatiebewaking'.

ATC Codes			'Commentaren Medicatiebewaking' edition																				
			99/00	00/01	01/02	02/03	03/04	04/05	05/06	06/07	07/08	08/09	09/10	10/11	11/12	12/13	13/14	14/15	15/16	16/17	17/18	18/19	19/20	20/21
N05A Antipsychotics/Neuroleptic																								
1	N05AD01	Haloperidol	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
2	N05AH04	Quetiapine				B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
3	N05AN01	Lithium	D	D	D	D	D	D	D	D	D	T	T	T	T	T	T	T	T	T	T	T	T	RA
4	N05AH03	Olanzapine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
5	N05AX08	Risperidone	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
6	N05AB04	Prochlorperazine																						
7	N05AD05	Pipamperone	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
8	N05AG02	Pimozide	B1	B1	B1	B1	B1	B1	B1	B1	B1	O	O	O	O	O	O	O	O	O	O	O	O	O
9	N05AF03	Chlorprothixene																						
10	N05AX12	Aripiprazole							B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
11	N05AH02	Clozapine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
12	N05AC02	Thioridazine	B	B	B	B	B	B	B	B	B													
13	N05AF01	Flupentixol	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
14	N05AA02	Levomepromazine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O							
15	N05AF05	Zuclopenthixol	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
16	N05AB02	Fluphenazine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
N05B Anxiolytics/Tranquilizers																								
1	N05BA04	Oxazepam	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
2	N05BA01	Diazepam	B	B	B	B	B	B	B	B	C	O	O	O	O	O	O	O	O	O	O	O	O	WO (1e/2e) MR (3e)
3	N05BA12	Alprazolam	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WO (1e/2e) MR (3e)
4	N05BA06	Lorazepam	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
5	N05BB01	Hydroxyzine	B	B	B	B	B	B	A	B	B	O	O	O	O	O	O	O	O	O	O	O	O	
6	N05BA09	Clobazam	B	B	B	B	B	B	B	B	B	O	O	B	B	B	B	B	B	B	B	B	O	O
7	N05BA05	Potassium clorazepate	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
8	N05BA08	Bromazepam	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
9	N05BA02	Chlordiazepoxide	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	

10	N05BE01	Buspirone	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O

N05C Hypnotics and sedatives

1	N05CD07	Temazepam	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
2	N05CF02	Zolpidem	B	B	B	B	B	B	B	B	B	O	O	O	O	O	F	F	F	F	F	F	WO (1e/2e) MR (3e)
3	N05CD06	Lormetazepam	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O
4	N05CF01	Zopiclone	B	B	B	B	B	B	B	B	B	O	O	O	O	O	F	F	F	F	F	F	WO (1e/2e) MR (3e)
5	N05CM09	Valerianae radix	A	A	A	A	A	A	A	A	A	R	R	R	R	R	R	R	R	R	R	R	WO
6	N05CD08	Midazolam	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O
7	N05CD01	Flurazepam	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O
8	N05CD02	Nitrazepam	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O
9	N05CH01	Melatonin										O	O	O	O	O	O	O	O	O	O	O	O

N06A Antidepressants

1	N06AB05	Paroxetine	B	B	B	B	B	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
2	N06AB04	Citalopram				B	B	B	B	C	C	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
3	N06AB03	Fluoxetine	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
4	N06AB06	Sertraline	B	B	B	B	B	B	B	C	C	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
5	N06AX16	Venlafaxine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	F	F	F	F	F	WV (1e/2e) MR (3e)
6	N06AA09	Amitriptyline	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
7	N06AA04	Clomipramine	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
8	N06AB08	Fluvoxamine	B1	B1	B1	B1	B1	B1	B1	B1	B1	O	O	O	O	O	F	F	F	F	F	F	WV (1e/2e) MR (3e)
9	N06AB10	Escitalopram							B	B	B	O	O	O	O	O	F	F	F	F	F	F	WV (1e/2e) MR (3e)
10	N06AX11	Mirtazapine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	MR (3e)
11	N06AX21	Duloxetine								B	B	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)

12	N06AA10	Nortriptyline	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
13	N06AX12	Bupropion								B1	B1	O	O	O	O	O	O	F	F	F	F	F	F	WV (1e/2e) MR (3e)
14	N06AX25	Hyperici herba					B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
15	N06AA21	Maprotiline	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
16	N06AX05	Trazodone	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O (1e/2e) MR (3e)
17	N06AG02	Moclobemide	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
18	N06AX06	Nefazodone				B	B																	
19	N06AA02	Imipramine	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
20	N06AA06	Trimipramine	B	B	B	B	B	B	B															
N06B Psychostimulants																								
1	N06BA04	Methylphenidate				B2	B2	B2	B2	B2	B2	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e) O (2e/3e)
2	N06BA07	Modafinil					B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	TN	RA
3	N06BC01	Caffeine																						
4	N06BA02	Dexamphetamine															O	O	O	O	O	O	MR	
N07B Parasympathomimetica																								
1	N07AA02	Pyrodistigmine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
2	N07AA03	Distigmine	B	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
N07B Anti-addictives																								
1	N07BA01	Nicotine	D	D	D	D	D	D	D	D	D	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	MR
2	N07BA03	Varenicline										O	O	O	O	O	O	O	O	O	O	O	O	WV
3	N07BB01	Disulfiram	B3	B3	B3	B3	B3	B3	B3	B3	B3	O	O	O	O	O	O	O	O	O	O	O	O	O
4	N07BC02	Methadone	C	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	MR
N07C Antivertigo																								
1	N07CA01	Betahistine					B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
2	N07CA02	Cinnarazine	B2	B2	B2	B2	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
3	N07CA03	Flunarizine					B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O

N07X Other NS drugs																							
1	N07XX04	Sodium oxybate															O	O	O	O	O	O	O
2	N07XX07	Fampridine															O	O	O	O	O	O	O

The letters A, B(1,2,3), C and D are the safety classes in Commentaren Medicatiebewaking editions 1999-2008. F=pharmacological effect(s); monitor during use. O=insufficient experience, risk is unknown. R=broad experience, can be used. T= teratogenic effect(s); monitor during use. FN= pharmacological effect(s), do not use (temporarily). TN= teratogenic effect(s); do not use (temporarily). WO=most safe/probably safe under certain conditions. MR= potential risks. WV= probably safe. RA= risk at birth defects.

*Adapted from 'Commentaren Medicatiebewaking' editions 1999/2000 until edition 2020/*2021.

Table 8: Safety classification adjustments 2000-2010 in CM per year, per drug with underlying motivation.

Safety Classification Adjustments 2000-2021			
Year	ATC	Adjustment(s):	Underlying reason(s) based on information in CM or via literature research:
2000/2001		No adjustments made.	
2001/2002		No adjustments made.	
2002/2003		No adjustments made.	
2003/2004	N05AN01	Lithium is classified in the class of antipsychotics for the first time and is removed from the class of antidepressants.	The change is due to a labelling change.
2004/2005	R06AA02/ D04AA33/ D04AA32	Diphenhydramine was adjusted from the old classification of B into the new classification of A. Diphenhydramine is categorized in the class Hypnotics, sedatives and anxiolytics. It is used to aid sleep disorders.	Before 2004, diphenhydramine was only mentioned in the class of the hypnotics and sedatives. As per 2004/2005, diphenhydramine was also mentioned in the antihistaminica and fluorescence ophthalmologicals. For a drug to be placed into category A, at least 1000 cases should be present without mentioning of side effects. As per 2004 the drug is used as an antihistaminic and ophthalmologic, it is possibly to say that the number of cases increased drastically, causing the drug to be placed in the category A.
	N06AB05	Paroxetine was adjusted from the old classification of B into the new classification of C. Paroxetine is categorized in the class of Antidepressants. It is a SSRI.	'Commentaren Medicatiebewaking' from editions 2003/2004 and 2004/2005 mention that reasonable experience is found and that the use of SSRI's may lead to withdrawal symptoms in the neonate. However, the 2003/2004 edition says that more information is needed for a definite risk assessment. This statement is not mentioned in edition 2004/2005, meaning that enough information is gained to classify sertraline in the classification of C.
2005/2006	N05BB01	Hydroxyzine was adjusted from the old classification of B into the new classification of A. Hydroxyzine is categorized in the class of Hypnotics, sedatives and anxiolytics.	'Commentaren Medicatiebewaking' 2005/2006 mentions that due to the analogue of antihistaminica in an allergic condition, the drug is adjusted from classification B into classification A. Hydroxyzine is a H_1-receptor antagonist used as an anxiolytic and antihistaminic.[42] In 'Commentaren Medicatiebewaking' 2005/2006 it is said that in humans no signs of increased prevalence of birth defects are seen for the old, often used antihistaminica. Hydroxyzine is an old, often used antihistaminica and therefore the classification of B has been adjusted into the classification of A, due to the analogue of the use of the antihistaminic.
2006/2007	N05BB01	Hydroxyzine was adjusted from the old classification of A into the new classification of B.	'Commentaren Medicatiebewaking' 2006/2007, has categorized hydroxyzine in classification B again. This might have to do with the fact old medicines, which have been used a lot and did not led to an increased prevalence of birth defects, are categorized in

		classification A. However, there has never been found supporting literature with controlled human studies to support the classification of A for these drugs. Hence, it is decided to place these drugs in classification of B.
N06AB06	Sertraline was adjusted from the old classification of B into the new classification of C. Sertraline is categorized in the class of antidepressants. It is an SSRI.	At the end of 2005 and beginning of 2006, there have been multiple publications suggesting an association of the use of an SSRI and harmful pharmacological effects in the unborn child. An example of such a publication is the study of Gentile et al.[43] Hence, in the edition of 'Commentaren Medicatiebewaking' 2006/2007 sertraline is categorized in the classification of C, due to its association with pharmacological effects in the unborn child.
N06AB04	Citalopram was adjusted from the old classification of B into the new classification of C. Citalopram is categorized in the class of antidepressants. It is an SSRI.	'Commentaren Medicatiebewaking' edition 2005/2006 mentions that limited experience with the use of citalopram is occurring, hence sufficient data is missing for a definite risk classification. In 2006/2007, the 'Commentaren Medicatiebewaking' mentions that broad experience with the use of citalopram is gained. In addition, at the end of 2005 and the beginning of 2006, there have been multiple publications suggesting an association of the use of an SSRI and harmful pharmacological effects in the unborn child. This statement is supported by the study of Eydie et al.[44] This statement is however not supported by publications from Gentile et al or Sivojelezova et al.[43,45] It is plausible to change the classification when a study has shown increased prevalence of risks to the neonate. It might also be possible the classification is changed due to the development of withdrawal symptoms in the neonate connected to SSRI use during pregnancy.
A03BA01	Atropine was adjusted from the old classification of A into the new classification of C. Atropine is categorized in the class of spasmolytics.	In the 'Commentaren Medicatiebewaking' 2006/2007, it says that parasympatholytics like atropine can influence the heartbeat of the foetus due to pharmacological effects, but that still limited documentation is available. These statements are also made in the 2005/2005 edition of 'Commentaren Medicatiebewaking', as this side effect was already described in 1981 by a study conducted by Murad et al.[46]
A03AD01	Papaverine was adjusted from the old classification of A into the new classification of B. Papaverine is categorized in the class of spasmolytics.	Publications of papaverine are already found in the 1870s.[47] For the old drugs, which have no available literature on pharmacological or teratogenic effects, it was possible to find these in the classification of A. These had been used for many years without any publications on their side effects, hence they were considered to be fitting in classification A. Later on, there was unease to classify drugs in classification A, without having any

			documentation about their safety. Therefore, the older drugs with limited documentation were reclassified in classification B.
2007/2008	N03AE01	Clonazepam was adjusted from the old classification of B into the new classification of C. Clonazepam is categorized in the class of benzodiazepines in the hypnotics, sedatives and anxiolytics.	'Commentaren Medicatiebewaking' 2007/2008 mentions that short use of benzodiazepines prenatal may result in floppy infant syndrome and long-use of benzodiazepines may lead to withdrawal symptoms in the neonate. This statement was supported by the publication of Emilio et al.[44] This new information led to the reclassification of clonazepam into the classification of C. The findings were also supported in latter publications, by for example the study of Murray et al.[48]
	N05BA01	Diazepam was adjusted from the old classification of B into the new classification of C. Diazepam is categorized in the class of benzodiazepines in the hypnotics, sedatives and anxiolytics.	'Commentaren Medicatiebewaking' 2007/2008 mentions that short use of benzodiazepines prenatal may result in floppy infant syndrome and long-use of benzodiazepines may lead to withdrawal symptoms in the neonate. This statement was supported by the publication of Emilio et al.[57;44] This new information led to the reclassification of clonazepam into the classification of C. The findings were also supported in latter publications, by for example the 'Geneesmiddelen Informatie Bank'.[49]
2008/2009	N03AE01	Clonazepam was adjusted from the old classification subject-matter of C into the new classification subject-matter of O. Clonazepam is categorized in the class of benzodiazepines in the hypnotics, sedatives and anxiolytics.	Clonazepam has been adjusted from the safety classification of *pharmacological effects* into the safety classification that the risk of clonazepam use during pregnancy is not known. It is possible to say this has to do that studies are controversial. This is also mentioned in the textbook 'Commentaren Medicatiebewaking': no unambiguous findings exist. It might be due to the controversy is chosen to place diazepam in safety classification O; the risk is not known.
	N05BA01	Diazepam was adjusted from the old classification subject-matter of C into the new classification subject-matter of O. Diazepam is categorized in the class of benzodiazepines in the hypnotics, sedatives and anxiolytics.	Diazepam has been adjusted from the safety classification of *pharmacological effects* into the safety classification that the risk of diazepam use during pregnancy is not known. It is possible to say this has to do with the fact that studies are controversial. This controversy is also discussed in the study of Dorte et al.[50] Some studies show an association of harm to the embryonic development due to pharmacological effects, whereas some studies do not. It might be due to the controversy is chosen to place diazepam in safety classification O; the risk is not known.
2009/2010		No adjustments made.	
2010/2011		No adjustments made.	

2011/2012		No adjustments made.	
2012/2013		No adjustments made.	
2013/2014	N05CF02	Zolpidem was adjusted from the old classification of O into the new classification of F. Zolpidem is categorized in the class of benzodiazepines in the hypnotics, sedatives and anxiolytics.	Zolpidem and zopiclone have been adjusted from the category *risk unknown* into *pharmacologic effect, monitor during use*. The 2012/2013 edition of 'Commentaren Medicatiebewaking' states that the experience of zolpidem and zopiclone was limited during pregnancy, therefore, no comments could be made about the possible risk. In next year's edition of the book, 2013/2014, states that an acceptable amount of experience regarding the use of these drugs during pregnancy is gained. Additionally, no clear indications that may lead to an increase rate of birth defects or other disadvantageous effects were found. This is also supported in literature; Wikner et al. found no evidence of an increased malformation rate among 1381 pregnant women.[51]
	N05CF01	Zopiclone was adjusted from the old classification of O into the new classification of F. Zopiclone is categorized in the class of benzodiazepines in the hypnotics, sedatives and anxiolytics.	
	N06AB10	Escitalopram was adjusted from the old classification of O into the new classification of F. Escitalopram is categorized as an SSRI in the antidepressants.	Escitalopram has been adjusted from the category *risk unknown* into the category *pharmacological effect; monitor during use*. In the 2012/2013 edition of the textbook 'Commentaren Medicatiebewaking', is stated that the experience with escitalopram is >600 pregnancies. Moreover, it stated that no reasons are found to assume a substantially increased risk on congenital disorders associated with SSRI exposure during pregnancy. Though, possibilities on developing specific birth defects due to the use of SSRIs, could not be ruled out, the absolutive risk is limited to a minimum, as the prevalence of the specific birth defects is rather low. In the case of long-term use, the new-born infant may suffer from withdrawal symptoms. In the 2013/2014 edition, the experience regarding the use of escitalopram has been increased to more than 1200 pregnancies. Furthermore, it states that recent literature is contradictive, though, majority of the studies involving SSRIs did not observe any increased risks on birth defects. C. Bellantuono et al reviewed 12 separate studies which assessed the possible risks associated with escitalopram use. All studies failed to demonstrate a significant risk on major malformations linked to the use of escitalopram. Though, an elevated risk on perinatal complications such as low birth weights, spontaneous abortion symptoms or withdrawal symptoms could not be ruled out.[52]
	N06AB08	Fluvoxamine was adjusted from the old classification of O into the new classification of F. Fluvoxamine is categorized as an SSRI in the antidepressants.	In the 2012/2013 edition of 'Commentaren Medicatiebewaking', the experience with the use of fluvoxamine is described as reasonable (>600 pregnancies exposed to fluvoxamine). In the next edition, 2013/2014, fluvoxamine was used in more than 700 pregnancies. As

			described for escitalopram, 'Commentaren Medicatiebewaking' states that SSRIs are generally not associated with congenital disorders, though there are reports of new-borns suffering from withdrawal symptoms. Therefore, the safety classification has been changed.
2014/2015	N06AX12	Bupropion was adjusted from the old classification of O into the new classification of F. Bupropion is categorized as other in the antidepressants and as an anti-addictive.	The 2013/2014 edition of 'Commentaren Medicatiebewaking, mentions that little experience regarding the use during pregnancy is found. Nevertheless, no significant increased risks of birth defects or any other adverse effects on the pregnancy itself or the offspring were found. However, there were indications that the use may lead to congenital heart defects. In the 2014/2015 edition, 'Commentaren Medicatiebewaking' states that the broad experience of use of bupropion did not show any leads of an increased risk of congenital defects, heart defects or any other disadvantageous effects. Therefore, bupropion was now classified in category '*pharmacological effect, monitor during use*'. Though, literature is contradictive; some studies still claim to have found an increased risk of congenital heart defects when using bupropion, while others do not. Cole et al[53] have found no increased prevalence of congenital defects related to the use of bupropion in the first trimester. On the other hand, Thyagarajan et al[54] describe an increased occurrence of left ventricular outflow tract obstruction (LVOTO) among offspring of bupropion users, in comparison to the use of other antidepressants.
	N06AX16	Venlafaxine was adjusted from the old classification of O into the new classification of F. Venlafaxine is categorized as other in the antidepressants.	'Commentaren Medicatiebewaking', the 2013/2014 edition, mentions that the broad experience regarding the use of venlafaxine did not show any increased risks of congenital defects. Though, long-term use may cause the neonate to experience withdrawal symptoms (e.g., hypertonia, tremors, irregular breathing). In the 2014/2015 edition, venlafaxine was classified in the category *pharmacological effect, monitor during use* instead of *insufficient experience, risk unknown*.
2015/2016		No adjustments made.	
2016/2017		No adjustments made.	
2017/2018		No adjustments made.	
2018/2019		No adjustments made.	

2019/2020	N06BA07	Modafinil was adjusted from the old classification of O into the new classification of TN. Modafinil is categorized as a psychostimulant.	In the 2018/2019 edition of 'Commentaren Medicatiebewaking', it is stated that no or highly insufficient experience regarding the use of modafinil during pregnancy is occurring. As a result, the drug was placed in the category *insufficient experience, risk unknown.* One year later, in the 2019/2020 edition, modafinil was classified in the category *teratogenic, do not* use. Though there was still limited information available about the use of modafinil during pregnancy, the manufacturer found an increased risk on congenital disorders as well as heart failures. Moreover, growth retardation was often reported. Therefore, 'Commentaren Medicatiebewaking' highly discourages the use of modafinil during pregnancy.
2020/2021	R06AA02	Diphenhydramine was adjusted from the old classification of R, into the new classification of O.	In the 2019/2020 edition of 'Commentaren Medicatiebewaking', it is stated that the use of diphenhydramine during pregnancy should last for a short period of time and when used, in a low dose. The 2020/2021 edition of the CM only refers to the website of TIS for more information. Only TIS does not provide any information about diphenhydramine use during pregnancy. The change in safety classification of this drug thus cannot be determined.
	N06AX11	Mirtazapine was adjusted from the old classification of O into the new classification of MR (3rd).	In the 2019/2020 edition of 'Commentaren Medicatiebewaking', it is stated that reasonable experience has been gained about the use of mirtazapine during pregnancy, and the experience does not result in an increased incidence of birth defects. In the 2020/2021 edition, the CM refers to the TIS website. On the website, mirtazapine is said to have possible risks when used in the 3rd trimester. However, TIS also says that studies about the use of mirtazapine during pregnancy does not show a higher incidence of birth defects. It is however known that the use of antidepressants leads to withdrawal symptoms in the neonate. It is therefore chosen, based on the knowledge about general antidepressant use during the pregnancy, to place mirtazapine in the MR safety class.
	N06BA02	Dexamphetamine was adjusted from the classification of O into the new classification of MR.	In the 2019/2020 edition of 'Commentaren Medicatiebewaking', it is stated that no or insufficient experience with dexamphetamine during pregnancy is available. The 2020/2021 edition refers to the TIS website for more information. This website states that studies have been conducted, with over 7000 pregnancies exposed to dexamphetamine during the first trimester, which did not show an increased incidence at birth defects or heart defects. However, information about dexamphetamine in the second and third trimester is missing. On the other hand, information about the use of amphetamine during the whole pregnancy is available. The use of amphetamine resulted in a higher risk at prebirth and growth and weight problems in the neonate. In addition, the use of

		psychostimulants can result in withdrawal symptoms in the new-born. Therefore, it was chosen to adjust dexamphetamine to the safety class of MR.
N07BA01	Nicotine was adjusted from the old classification of TN, into the new classification of MR.	In the 2019/2020 edition of 'Commentaren Medicatiebewaking' it is said that nicotine exposure during pregnancy increases the risks of miscarriages, growth retardation, low birth weight and cot death. These are teratogenic effects, hence the classification for nicotine as TN was chosen. The exposure to nicotinic preparations, like nicotinic plasters, during pregnancy has limited experience. The 2020/2021 CM edition refers to the website of TIS. Where it is also stated that the experience with nicotinic preparations is limited. This might be the reason that nicotine has been adjusted. Reason is not mentioned.
N07BA03	Varenicline was adjusted from the old classification of O into the new classification of WV.	In the 2019/2020 edition of 'Commentaren Medicatiebewaking' is stated that varenicline use during pregnancy has limited available data to give a significant statement about its safety to use during pregnancy. The 2020/2021 edition of CM refers to TIS for background information. On the TIS website is stated that experience is gained from approximately 1000 first trimester pregnancies exposed to varenicline. This gain in information did not result in an increased incidence of birth defects. This gain in experience is also seen in a study from Richardson et al, which also showed not an increased incidence in congenital malformations upon varenicline exposure in the first trimester.[55] This led to the adjustment of the safety classification of varenicline.

ATC N05 stands for the psycholeptics. ATC N06 stands for the psychoanaleptics. ATC code N07 stands for other various nervous system targeting drugs. ATC R0 stands for respiratory system targeting drugs. ATC D0 stands for dermatologics. ATC A03 is for drugs targeting functional gastrointestinal disorders. The letters displayed in the 'change' column are explained in the method section.

*Adapted from 'Commentaren Medicatiebewaking' editions 1999/2000 until edition 2020/*2021 and https://www.lareb.nl/tis-knowledge.

Introduction and withdrawal of psychotropic drugs from Commentaren Medicatiebewaking from Health Base between 2000-2021

Various drugs have been introduced and withdrawn from classification in the CM. An overview of these drugs can be found in ***Appendix 3***.

Overview of the changes in classification of drugs used during pregnancy based on Commentaren Medicatiebewaking from Health Base

An overview of the adjusted classifications of the drugs and the reason behind the change can be seen in *Table 9.*

Table 9: Overview of the changes in classification of drugs used during pregnancy based on Commentaren Medicatiebewaking from Health Base.

Year	ATC	Drug	Change	Classification of the changes
2003/2004	N05	Lithium	N06→N05	Labelling change
2004/2005	R0/D0	Diphenhydramine	B→A	Increased experience
	N06	Paroxetine	B→C	Increased experience
2005/2006	N05	Hydroxyzine	B→A	Miscellaneous
2006/2007	N05	Hydroxyzine	A→B	Old, extensively used drug
	N06	Sertraline	B→C	New available studies
	N06	Citalopram	B→C	Increased experience
	A03	Atropine	A→C	New available studies
	A03	Papaverine	A→B	Old, extensively used drug
2007/2008	N03	Clonazepam	B→C	New available studies
	N05	Diazepam	B→C	New available studies
2008/2009	N03	Clonazepam	C→O	New available studies
	N05	Diazepam	C→O	New available studies
2013/2014	N05	Zolpidem	O→F	Increased experience
	N05	Zopiclone	O→F	Increased experience
	N06	Escitalopram	O→F	Increased experience
	N06	Fluvoxamine	O→F	Increased experience
2014/2015	N06	Bupropion	O→F	New available studies
	N06	Venlafaxine	O→F	New available studies
2019/2020	N06	Modafinil	O→TN	Labelling change
2020/2021	R0	Diphenhydramine	R→O	Miscellaneous
	N06	Mirtazapine	O→MR	Miscellaneous
	N06	Dexamphetamine	O→MR	Miscellaneous
	N07	Nicotine	TN→MR	Miscellaneous
	N07	Varenicline	O→WV	Increased experience

ATC N05 stands for the psycholeptics. ATC N06 stands for the psychoanaleptics. ATC code N07 stands for other various nervous system targeting drugs. ATC R0 stands for respiratory system targeting drugs. ATC D0 stands for dermatologics. ATC A03 is for drugs targeting functional gastrointestinal disorders. The letters displayed in the 'change' column are explained in the method section.

As can be seen, there are some drugs that are outside the ATC classes N05, N06 and N07.

Categorization of changes of classification of drugs used during pregnancy based on Commentaren Medicatiebewaking from Health Base

Following the categorization of the changes behind the adjustments of safety classification of the drugs, *Table 10* is made.

Table 10: Number of changes per category of reason behind the change per ATC code.

Category	**1**: new available studies	**2**: increased experience	**3**: labelling change	**4**: old, extensively used drug	**5**: miscellaneous	*Total*
N05	2	2	1		2	7
N06	3	4	1		2	10
N07		1			1	2
Total	5	7	2		5	19

Comparison between ATC classes

The differences in the observed number of classification changes within a specific ATC class versus the other psychotropic drugs are discussed separately.

Comparison of psycholeptics (N05) with other psychotropic drugs (N06 and N07)

Table 11: 2x2 crosstab of comparison psycholeptics (N05) with other psychotropic drugs (N06 and N07).

Category	Number changed safety classifications	Number of unchanged safety classifications	Total	p-value	OR
Psycholeptics (N05)	*7*	*70*	*77*	*0.041*	*0.33*
Other psychotropics (N06 and N07)	*12*	*40*	*52*		
Total	*19*	*110*	*129*		

The number of safety classification changes in N05 was significant lower compared to the safety classification changes in N06 plus N07. ($X^2(1)>4.834$, p = 0.041). The crude odds ratio= ((7/70)/(12/40))= 280/840=0,33. This supports the statement that there are indeed less changes in N05 versus the rest of his group.

Comparison of psychoanaleptics (N06) with other psychotropic drugs (N05 and N07).

Table 12: 2x2 crosstab of comparison psycholeptics (N05) with other psychotropic drugs (N05 and N07).

Category	Number changed safety classifications	Number of unchanged safety classifications	Total	p-value	OR
Psychoanaleptics (N06)	*10*	*29*	*39*	*0.030*	*3.10*
Other psychotropics (N05 and N07)	*9*	*81*	*90*		
Total	*19*	*110*	*129*		

The number of safety classification changes in N06 was significant higher compared to the safety classification changes in N05 plus N07. ($X^2(1)>5.300$, p = 0.030). The crude odds ratio= ((10/29)/(9/81))= 810/261=3.10. This supports the statement that there are indeed more changes in N06 versus the rest of his group.

Comparison of various nervous system drugs (N07) with other psychotropic drugs (N05 and N06)

Table 13: 2x2 crosstab of comparison psycholeptics (N05) with other psychotropic drugs (N05 and N06).

Category	Number changed safety classifications	Number of unchanged safety classifications	Total	p-value	OR
Various NS targeting drugs (N07)	*2*	*11*	*13*	*1.000*	*1.06*
Other psychotropics (N05 and N06)	*17*	*99*	*116*		
Total	*19*	*110*	*129*		

The number of safety classification changes in N07 is not significant different compared to the safety classification changes in N05 plus N06. ($X^2(1)>0.005$, p = 1). The crude odds ratio= ((2/11)/(17/99))= 198/187=1.06. This tells that the number of changes in N07 is higher compared to the other psychotropic drugs (N05 and N07), although it is not significant higher.

Comparison between the first and second decade

Comparison of first decade vs second decade of psycholeptics (N05) with other psychotropics (N06 and N07).

Table 14: 2x2 crosstab of comparison first decade vs second decade of psycholeptics (N05) with other psychotropic drugs (N06 and N07).

Category	First decade (2000-2010)	Second decade (2010-2021)	Total	p-value	OR
Psycholeptics (N05)	*5*	*2*	*7*	*0.074*	*7.5*
Other psychotropics (N06 and N07)	*3*	*9*	*12*		
Total	*8*	*11*	*19*		

The number of safety classification changes between the first and second decade for the psycholeptics (N05) is not significant different compared to the safety classification changes between the first and second decade for the other psychotropics (N06 and N07). ($X^2(1)>3.909$, p = 0.074). The crude odds ratio= ((5/2)/(3/9))=45/6=7.5. This tells that more changes in the psycholeptics (N05) have occurred in the first decade compared to the changes of the other psychotropics (N06 and N07), although the difference is not statistically significant.

Comparison of first decade vs second decade of psychoanaleptics (N06) with other psychotropics (N05 and N07).

Table 15: 2x2 crosstab of comparison first decade vs second decade of psychoanaleptics (N06) with other psychotropic drugs (N05 and N07).

Category	First decade (2000-2010)	Second decade (2010-2021)	Total	p-value	OR
Psychoanaleptics (N06)	3	7	*10*	*0.370*	*0.343*
Other psychotropics (N05 and N07)	5	4	*9*		
Total	*8*	*11*	*19*		

The number of safety classification changes between the first and second decade for the psychoanaleptics (N06) is not significant different compared to the safety classification changes between the first and second decade for the other psychotropics (N05 and N07). ($X^2(1)>1.626$, p = 0.370). The crude odds ratio= ((3/7)/(5/4))=12/35=0.343. This tells that less changes in the

psychoanaleptics (N06) have occurred in the first decade compared to the changes of the other psychotropics (N05 and N07), although the difference is not statistically significant.

Comparison of first decade vs second decade of various CNS targeting drugs (N07) with other psychotropics (N05 and N06).

Table 16: 2x2 crosstab of comparison first decade vs second decade of various CNS targeting drugs (N07) with other psychotropic drugs (N05 and N06).

Category	First decade (2000-2010)	Second decade (2010-2021)	Total	p-value	OR
Various NS-targeting drugs (N07)	*0*	*2*	*2*	*0.485*	*0.224*
Other psychotropics (N05 and N06)	*8*	*9*	*17*		
Total	*8*	*11*	*19*		

The number of safety classification changes during 2000-2010 in N07 is not significant different compared to the safety classification changes during 20010-2020 in N05 and N06. ($X^2(1)>1.626$, p = 0.485). Calculation of the crude OR results in an infinite number, hence the Haldane-Anscombe correction was done. The crude odds ratio= ((0.5/2.5)/(8.5/9.5))=4.75/21.25=0.224. This tells that less changes in the various CNS targeting drugs (N07) have occurred in the first decade compared to the changes of the other psychotropics (N05 and N06), although the difference is not statistically significant.

Comparison between the nature of the change

Comparison of the number of *new studies* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psycholeptics (N05) compared with other psychotropics (N06 and N07).

Table 17: 2x2 crosstab of number of new studies and number of other natures of change in the psycholeptics (N05) compared to the number of new studies and number of other natures of change in other psychotropics (N06 and N07).

Category	New studies as nature of change	Other natures of change	Total	p-value	OR
Psycholeptics (N05)	2	5	*7*	*1.000*	*1.2*
Other psychotropics (N06 and N07)	3	9	*12*		
Total	*5*	*14*	*19*		

The number of safety classification changes in category *new studies* in N05 is not significant different compared to the safety classification changes in the other categories in N06 and N07. ($X^2(1)>0.029$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((2/5)/(3/9))=18/15=1.2. This tells that the motivation consisting of new studies behind an adjustment is higher in the psycholeptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *increased experience* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psycholeptics (N05) compared with other psychotropics (N06 and N07).

Table 17: 2x2 crosstab of number of increased experience and number of other natures of change in the psycholeptics (N05) compared to the number of increased experiences and number of other natures of change in other psychotropics (N06 and N07).

Category	Increased experience as nature of change	Other natures of change	Total	p-value	OR
Psycholeptics (N05)	*2*	*5*	*7*	*0.656*	*0.56*
Other psychotropics (N06 and N07)	*5*	*7*	*12*		
Total	*7*	*12*	*19*		

The number of safety classification changes in category 'increased experiences' in N05 is not significant different compared to the number of safety classification changes in the other categories in N06 and N07. ($X^2(1)>0326$, p = 0.656). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((2/5)/(5/7))=14/25=0.56. This tells that the motivation consisting of increased experience behind an adjustment is lower in the psycholeptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *labelling change* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psycholeptics (N05) compared with other psychotropics (N06 and N07).

Table 18: 2x2 crosstab of number of labelling change and number of other natures of change in the psycholeptics (N05) compared to the number of labelling change and number of other natures of change in other psychotropics (N06 and N07).

Category	Labelling change as nature of change	Other natures of change	Total	p-value	OR
Psycholeptics (N05)	*1*	*6*	*7*	*1.000*	*1.83*
Other psychotropics (N06 and N07)	*1*	*11*	*12*		
Total	*2*	*17*	*19*		

The number of safety classification changes in category 'labelling change' in N05 is not significant different compared to the number of safety classification changes in the other categories in N06 and N07. ($X^2(1)>0.166$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((1/6)/(1/11))=11/6=1.833. This tells that the motivation consisting of a label change behind an adjustment is higher in the psycholeptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *miscellaneous* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psycholeptics (N05) compared with other psychotropics (N06 and N07).

Table 20: 2x2 crosstab of number of miscellaneous and number of other natures of change in the psycholeptics (N05) compared to the number of miscellaneous and number of other natures of change in other psychotropics (N06 and N07).

Category	Miscellaneous as nature of change	Other natures of change	Total	p-value	OR
Psycholeptics (N05)	2	5	*7*	*1.000*	*1.2*
Other psychotropics (N06 and N07)	3	9	*12*		
Total	*5*	*14*	*19*		

No significant difference between the nature 'miscellaneous' and the other natures in ATC class N05 compared to the changes from N06 and N07. ($X^2(1)> =0.029$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds

ratio= ((2/5)/(3/9))=18/15=1.2. This tells that the motivation consisting of miscellaneous reasons behind an adjustment is higher in the psycholeptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *new studies* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psychoanaleptics (N06) compared with other psychotropics (N05 and N07).

Table 9: 2x2 crosstab of number of new studies and number of other natures of change in the psychoanaleptics (N06) compared to the number of new studies and number of other natures of change in other psychotropics (N05 and N07).

Category	New studies as nature of change	Other natures of change	Total	p-value	OR
Psychoanaleptics (N06)	*3*	*7*	*10*	*1.000*	*1.5*
Other psychotropics (N05 and N07)	*2*	*7*	*9*		
Total	*5*	*14*	*19*		

No significant difference between the nature 'new studies' and the other natures in ATC class N06 compared to the changes from N05 and N07. ($X^2(1)> =0.148$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((3/7)/(2/7))=21/14=1.5. This tells that the motivation consisting of new studies behind an adjustment is higher in the psychoanaleptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *increased experience* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psychoanaleptics (N06) compared with other psychotropics (N05 and N07).

Table 10: 2x2 crosstab of number of increased experience and number of other natures of change in the psychoanaleptics (N06) compared to the number of increased experience and number of other natures of change in other psychotropics (N05 and N07).

Category	Increased experience as nature of change	Other natures of change	Total	p-value	OR
Psychoanaleptics (N06)	*4*	*6*	*10*	*1.000*	*1.33*
Other psychotropics (N05 and N07)	*3*	*6*	*9*		
Total	*7*	*12*	*19*		

No significant difference between the nature 'increased experience' and the other natures in ATC class N07 compared to the changes from N05 and N06. $X^2(1)> =0.166$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((4/6)/(3/6))=24/18=1.333. This tells that the motivation consisting of increased experience behind an adjustment is higher in the psychoanaleptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *labelling change* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psychoanaleptics (N06) compared with other psychotropics (N05 and N07).

Table 11: 2x2 crosstab of number of label changes and number of other natures of change in the psychoanaleptics (N06) compared to the number of label changes and number of other natures of change in other psychotropics (N05 and N07).

Category	Labelling change as nature of change	Other natures of change	Total	p-value	OR
Psychoanaleptics (N06)	*1*	*9*	*10*	*1.000*	*0.889*
Other psychotropics (N05 and N07)	*1*	*8*	*9*		
Total	*2*	*17*	*19*		

No significant difference between the nature 'labelling change' and the other natures in ATC class N06 compared to the changes from N05 andN07. $X^2(1)> =0.06$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((1/9)/(1/8))=8/9=0.889. This tells that the motivation consisting of a label change behind an adjustment is lower in the psychoanaleptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *miscellaneous* with the other nature of changes used as motivation behind the adjustment of the safety classification within the psychoanaleptics (N06) compared with other psychotropics (N05 and N07).

Table 12: 2x2 crosstab of number of miscellaneous and number of other natures of change in the psychoanaleptics (N06) compared to the number of miscellaneous and number of other natures of change in other psychotropics (N05 and N07).

Category	Miscellaneous as nature of change	Other natures of change	Total	p-value	OR
Psychoanaleptics (N06)	*2*	*8*	*10*	*0.628*	*0.5*
Other psychotropics (N05 and N07)	*3*	*6*	*9*		
Total	*5*	*14*	*19*		

No significant difference between the nature 'miscellaneous' and the other natures in the psychoanaleptics (N06) compared to the changes in the other psychotropics (N05 and N07). ($X^2(1)> =0.434$, p = 0.628). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((2/8)/(3/6))=12/24=0.5. This tells that the motivation consisting of miscellaneous reasons behind adjustments are lower in the psychoanaleptics compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *increased experience* with the other nature of changes used as motivation behind the adjustment of the safety classification within various CNS targeting drugs (N07) compared to other psychotropics (N05 and N06).

Table 13: 2x2 crosstab of number of increased experience and number of other natures of change in the various NS targeting drugs (N07) compared to the number of increased experience and number of other natures of change in other psychotropics (N05 and N06).

Category	Increased experience as nature of change	Other natures of change	Total	p-value	OR
Various NS targeting drugs (N07)	*1*	*1*	*2*	*1.000*	*1.83*
Other psychotropics (N05 and N06)	*6*	*11*	*17*		
Total	*7*	*12*	*19*		

No significant difference between the nature 'increased experience' and the other natures in ATC class N07 compared to the changes from N05 and N06. ($X^2(1)> =0.166$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((1/1)/(6/11))=11/6=1.833. This tells that the motivation consisting of increased experience behind adjustments are higher in the various CNS targeting drugs (N07) compared to the other psychotropics, although the difference is not statistically significant.

Comparison of the number of *miscellaneous* with the other nature of changes used as motivation behind the adjustment of the safety classification within various NS targeting drugs (N07) compared to other psychotropics (N05 and N06).

Table 14: 2x2 crosstab of number of miscellaneous and number of other natures of change in the various NS targeting drugs (N07) compared to the number of miscellaneous and number of other natures of change in other psychotropics (N05 and N06).

Category	Miscellaneous as nature of change	Other natures of change	Total	p-value	OR
Various NS targeting drugs (N07)	*1*	*1*	*2*	*1.000*	*3.25*
Other psychotropics (N05 and N06)	*4*	*13*	*17*		
Total	*5*	*14*	*19*		

No significant difference between the nature 'miscellaneous' and the other natures in ATC class N07 compared to the changes from N05 and N06. ($X^2(1)> =0.647$, p = 1.000). The nature thus had not a significant impact on the total number of changes and was not of great importance. The crude odds ratio= ((1/1)/(4/13))=13/4=3.25. This tells that the motivation consisting of miscellaneous reasons behind adjustments are higher for the various CNS targeting drugs (N07) compared to the other psychotropics, although the difference is not statistically significant.

Discussion and conclusions

In the Netherlands, the Teratologie Informatie Service, Health Base, Farmacotherapeutisch Kompas and some smaller units can be consulted for the safety of drug use during pregnancy. In addition, international safety classifications as for example the ADEC (Australia), FASS (Sweden), and FDA (America) are accessibly for information about the safety of drug use during pregnancy. This project has reviewed the advice of use of psychotropic drugs between 2000-2021 with help of the *Commentaren Medicatiebewaking* (CM) textbook, which was published annually by Health Base. The classification systems in the CM are based on the systems from TIS, ADEC and FASS. Some safety classification systems however have been subject to alternation.

For example, the categories in the systems of TIS, Health Base and FDA have been subject to changes. The motivation behind these alternations is akin for the various systems; at first, the categories had a limited description. This resulted in unclarity which practical consequences should be attached to the various codes. In addition, it was sometimes incorrectly assumed that the codes A to D indicated an increasing degree of severity of the effect, in which A was the safest and D the most unsafe. However, drugs categorized in class C are preferred over drugs categorized in class B. The implementation of descriptive categories and addition of categories solved these misconceptions and allowed health care professionals to choose a preference treatment. Although the adjustment of the system increased the comprehension of the categorization in the CM textbook, it gave rise to the methodological issue. When the advice regarding psychotropic drug use during pregnancy was studied between 2000-2021, it was important to distinguish between an adjustment in advice due to alternation of the system itself or due to for example an information gain about the safety of a drug.

To decipher the methodological problem, the subject-matters from the categories in the various classification systems were compared. Namely, if the subject-matter is the same, the categories can be aligned. This has for example been done for the categories: *B*, *insufficient experience; risk is unknown* and *unknown risks*. The alignment was made in accordance with TIS. If a drug was changed into a class outside the alignment, it was considered as a change in advice due to a reason beyond the alteration of the system itself. This alignment is feasible, but also had its limitation.

The change in safety classification itself made it harder to distinguish between a change due to an adjusted system or due to another nature of change. This has been tackled with the alignment table however it is possible a change has been missed.

Over the past two decades, a total of 25 safety classification changes have been observed. These changes fell outside the alignment table, which mean that the change had occurred due to another reason than a change in the safety classification system itself. However, not all of these 25 changes do consist of drugs that are categorized as N05, N06 nor N07. It is peculiar that these drugs are still classified in the CM as belonging to a psychotropic drug. This phenomenon might be due to a change in the ATC labelling of a drug. This however cannot be scrutinized as the ATC codes of these drugs are not mentioned in the CM from Health Base. As the change in ATC code cannot be confirmed, these adjustments in safety classification were not taken into account for the statistical tests. Therefore, a total of 19 classification changes is observed.

The total number of 19 classification changes for two decades provides information about the quality of the classification system in the CM textbook from Health Base. If only 19 changes have occurred in a time period of 20 years, a great majority of drugs in ATC class N05, N06 and N07 are classified accordingly over the past 20 years. From the nineteen changes, fifteen changes were into the safety class with pharmacological effects, thus safety classifications were directed into a more dangerous class. The adjustment of drugs, from which beforehand was unknown what effects they had upon exposure during pregnancy, into a class with the description of having pharmacological effects,

makes the whole classification system safer. All in all, the advice about use of psychotropic drugs in the CM textbook has been prudent and has become safer over the past two decades.

In addition, a pattern was observed as to the changes per year. The pattern consists of a period ranging from 2-6 consecutive years with adjustments of safety classes of drugs, followed by a period of time ranging from 4-5 years without any change in the safety classification of the drugs according to the 'Commentaren Medicatiebewaking' from Health Base. This pattern might have to do with the circumstances under which the textbook is made. It might be possible that Health Base follows protocols in which every 5 year a maintenance arises, which causes the number of safety classification adjustments to increase. It is also possible that in the years without adjustments, the drugs were classified accordingly and had no need to be adjusted.

By comparing the number of changed safety classifications of drugs with the number of drugs that do not have a changed safety classification, information about the fact that the specific ATC code has been exposed to a significant number of changes, or that the advice within an ATC code has not been changed over time was gained. For the psycholeptics (N05) was found that the class has been exposed to a significant lower number of safety classification changes when compared to the other psychotropics. For the psychoanaleptics (N06) was found that the class has been exposed to a significant higher number of safety classification changes when compared to the other psychotropics. The other nervous system targeting drugs (N07) showed to have a higher number of changes, however this difference was not statistically significant.

By comparing the number of changed safety classifications of drugs in the first decade (2000-2010) to the number of changed safety classifications of drugs in the second decade (2010-2021), no statistical difference was found for the psycholeptics, psychoanaleptics nor for the other nervous system targeting drugs. However, the credibility of the outcomes is debatable. As the values were low, the counts and minimum expected counts are below the criteria for the chi-square test. The outcome is thus based on little information.

By comparing the number of changes within a specific nature to the total number of changes of the ATC codes, information was gained whether a specific nature of change had a significant impact on the total number of changes. All the nature of changes, for the different ATC classes, did not have a significant impact on the total number of changes. However, the credibility of the outcomes is again debatable. As the values were low, the counts and minimum expected counts are below the criteria for the chi-square test. The outcome is thus based on little information.

Another limitation of the project is the fact that for some drugs, especially after implementation of system III, the reasons behind the change were unclear or could not even be found.

The strengths of the project were as follows: it was the first time this topic has been examined and the project covers a broad time span, namely a time span of 21 years. In addition, the whole class of psychotropic drugs is examined. Another strong point is the fact that not only the changes are made into an overview, but also the reasons behind the changes are examined, mapped and organized. At least, there was a great need to have this information resulting in a great significance of the study.

For further research, it is interesting to look into the effect of the trends in the advice with regard to the drug utilization. Hence, to see whether the change in advice has an impact on the prescription of the drug during pregnancy.

In conclusion, the number of classification changes between 2000-2021 was limited. From the total of nineteen changes, fourteen drugs had been changed from a classification in which the risks are not known, to a classification in which the drugs have pharmacological/ teratogenic effects. Thus, there seems to be a trend that the advice has become safer during the past two decades. The number of

changes in ATC class N05 was significantly lower, whereas number of changes in ATC class N06 was significantly higher, compared to the other psychotropics. The number of changes in the first decade (2000-2010) and second decade (2010-2021) did not show to have significant differences for the ATC classes. The number of specific nature of changes did not show to have a significant impact on the total number of changes in the ATC classes.

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Appendix

Appendix 1: Safety classification systems in Commentaren Medicatiebewaking

System I – until 07/08

categorie	betekenis (afhandeling)
A	Geen schadelijke effecten waargenomen in onderzoek bij zwangere vrouwen (veilig).
C	Farmacologische effecten waargenomen (of waarschijnlijk) bij foetus/neonaat, maar geen misvormingen. Geneesmiddelgebruik **afwegen***, bij voorkeur een veiliger geneesmiddel kiezen (categorie A).
D	Schadelijke effecten waargenomen (of waarschijnlijk); verhoogde kans op blijvende schade bij embryo/foetus. Geneesmiddelgebruik tijdens zwangerschap niet veilig! Zo mogelijk een veiliger geneesmiddel kiezen.
B	Mogelijke effecten onvoldoende bij de mens onderzocht. **B1**: geen schadelijke effecten waargenomen in onderzoek bij dieren. **B2**: mogelijke effecten onvoldoende bij dieren onderzocht . **B3**: schadelijke effecten bij dieren waargenomen . Geneesmiddelgebruik **afwegen***, bij voorkeur een geneesmiddel kiezen dat beter onderzocht is (categorie A of C).
NB: Een geneesmiddel in categorie B is per definitie niet veiliger dan in C. * Zie paragraaf *Praktische aanbevelingen*.	

System II – 08/09 until 19/20

Classificatie geneesmiddelen bij Zwangerschap	
categorie	**toelichting**
Ruime ervaring; kan gebruikt worden	Geneesmiddelen die in onderzoek of in de praktijk zijn gebruikt zonder dat er een verhoogde prevalentie van aangeboren afwijkingen dan wel andere directe of indirecte nadelige effecten op het embryo, de foetus of de pasgeborene zijn waargenomen. Geneesmiddel **kan gebruikt worden**.
Farmacol. effect; controle bij gebruik	Geneesmiddelen waarvan bekend is of kan worden vermoed dat zij farmacologische effecten bij het embryo, de foetus of de pasgeborene kunnen veroorzaken. Gebruik van geneesmiddel **afwegen**; bij gebruik controleren op nadelige effecten.
Farmacol. effect; (tijdelijk) niet gebruiken	Geneesmiddelen waarvan bekend is of kan worden vermoed dat zij farmacologische effecten bij het embryo, de foetus of de pasgeborene kunnen veroorzaken. Geneesmiddel tijdens risicovolle periode **niet gebruiken**;

	een ander geneesmiddel kiezen.
Teratogeen effect; controle bij gebruik	Geneesmiddelen waarvan bekend is of kan worden vermoed dat zij een verhoogde prevalentie van aangeboren afwijkingen of andere blijvende schade veroorzaken. Deze geneesmiddelen kunnen tevens nadelige farmacologische effecten op het embryo, de foetus of de pasgeborene hebben. Gebruik van geneesmiddel **afwegen**; bij gebruik controleren op ongewenste effecten.
Teratogeen effect; (tijdelijk) niet gebruiken	Geneesmiddelen waarvan bekend is of kan worden vermoed dat zij een verhoogde prevalentie van aangeboren afwijkingen of andere blijvende schade veroorzaken. Deze geneesmiddelen kunnen tevens nadelige farmacologische effecten op het embryo, de foetus of de pasgeborene hebben. Geneesmiddel **(tijdelijk) niet gebruiken**, in ieder geval tijdens risicovolle periode; ander geneesmiddel kiezen.
Onvoldoende ervaring; risico onbekend	Geneesmiddelen waarvan onvoldoende gegevens bekend zijn over het effect bij de mens om de risico's voor de zwangerschap en het ongeboren kind vast te stellen. Gebruik van geneesmiddel **afwegen**; bij voorkeur kiezen voor een geneesmiddel waarvan meer bekend is over de risico's.

System III - from 20/21 on

Classificatie geneesmiddelen bij Zwangerschap	
Categorie	**Toelichting**
Meest veilig	Dit geneesmiddel is - binnen de geneesmiddelgroep - de veiligste keuze voor gebruik tijdens de zwangerschap. Er is, in onderzoek of in de praktijk, geen verhoogd risico gevonden op aangeboren afwijkingen of andere nadelige effecten op de zwangerschap.
Waarschijnlijk veilig	Dit geneesmiddel kan gebruikt worden tijdens de zwangerschap. Indien beschikbaar, heeft een geneesmiddel uit de categorie 'Meest veilig' echter de voorkeur. Bijvoorbeeld omdat er meer onderzoek is gedaan naar dat middel.
Meest veilig / waarschijnlijk veilig onder voorwaarden	Indien aan de voorwaarde wordt voldaan kan dit middel veilig of waarschijnlijk veilig gebruikt worden tijdens de zwangerschap. Indien er een alternatief beschikbaar is uit de categorie 'Meest veilig' (eventueel onder voorwaarden), heeft dit wel de voorkeur.

Risico onbekend	Over gebruik van dit geneesmiddel tijdens de zwangerschap is geen of onvoldoende informatie beschikbaar. Het is niet mogelijk om een uitspraak te doen over de veiligheid. Kies bij voorkeur voor een middel waarvan meer bekend is over de veiligheid.
Mogelijk risico	Dit geneesmiddel kan mogelijk nadelige effecten hebben op de zwangerschap of het ongeboren kind. Weeg de mogelijke nadelige effecten af tegen het belang van behandeling van de moeder. Overweeg of een veiliger middel gebruikt kan worden of voer extra controles uit.
Risico op aangeboren afwijkingen	Dit geneesmiddel geeft een verhoogd risico op aangeboren afwijkingen of andere blijvende schade. Gebruik dit middel alleen in uitzonderingsgevallen (met extra controles). Kies zo mogelijk voor een veiliger middel of staak -tijdelijk- de behandeling.

Appendix 2: Safety classification of ATC classes N05, N06 and N07 according to Commentaren Medicatiebewaking from Health Base

Hypnotics, sedatives and anxiolytics

Hypnotics, sedatives and anxiolytics																						
year	*ATC code*	*00/01*	*01/02*	*02/03*	*03/04*	*04/05*	*05/06*	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*20/21*
Benzodiazepines																						
Lorazepam	N05BA56	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
Oxazepam	N05BA04	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
Temazepam	N05CD07	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
Alprazolam	N05BA12	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WO (1e/2e) MR (3e)
Bromazepam	N05BA08	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Brotizolam	N05CD09	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Chlordiazepoxide	N05BA02	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	
Clobazam	N05BA09	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Clonazepam	N03AE01				B	B	B	B	C	O	O	O	O	O	O	O	O	O	O	O	O	O
Clorazepinezuur	N05BA05	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Clotiazepam	N05BA21				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Cloxazolam	N05BA22				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	
Diazepam	N05BA01	B	B	B	B	B	B	B	C	O	O	O	O	O	O	O	O	O	O	O	O	WO (1e/2e) MR (3e)
Ethylloflazepaat	N05BA18				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Flunitrazepam	N05CD03	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Flurazepam	N05CD01	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Ketazolam	N05BA10	B	B	B	B	B	B	B	B													
Lormetazepam	N05CD06	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Loprazolam	N05CD11	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Medazepam	N05BA03	B	B	B	B	B	B															
Midazolam	N05CD08	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Nitrazepam	N05CD02	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Nordazepam	N05BA16	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Prazepam	N05BA11	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Tetrazepam	M03BX07				B	B	B	B	B	O	O	O	O	O	O							
Triazolam	N05CD05	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Zaleplon	N05CF03			B	B	B	B	B	B	O	O	O	O	O	O							
Zolpidem	N05CF02	B	B	B	B	B	B	B	B	O	O	O	O	O	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
Zopiclone	N05CF01	B	B	B	B	B	B	B	B	O	O	O	O	O	F	F	F	F	F	F	F	WO (1e/2e) MR (3e)
Other hypnotics and sedatives																						
Valerian radix	N05CM09	A	A	A	A	A	A	A	A	R	R	R	R	R	R	R	R	R	R	R	R	WO
Diphenhydramine	R06AA02				B	A	A	A	A	R	R	R	R	R	R	R	R	R	R	R	R	O
Buspirone	N05BE01	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Chloral hydrate	N05CC01				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Hydroxyzine	N05BB01	B	B	B	B	B	A	B	B	O	O	O	O	O	O	O	O	O	O	O	O	
Melatonin	N05CH01									O	O	O	O	O	O	O	O	O	O	O	O	O
Meprobamate	N05BC01				B	B	B	B	B	O	O	O	O	O	O	O	O						

F=farmacologisch effect, controle bij gebruik. O=onvoldoende ervaring, risico onbekend. R=ruime ervaring, kan gebruikt worden. T=teratogeen effect, controle bij gebruik. WO=waarschijnlijk veilig onder voorwaarden. MR=mogelijk risico. WV=waarschijnlijk veilig. RA=risico op aangeboren afwijking. TN=teratogeen effect, (tijdelijk) niet gebruiken. FN=farmacologisch effect, (tijdelijk) niet gebruiken. A/B(1,2,3)/C/D=Health Base classification 1999-2008.

Antipsychotics

Antipsychotics																						
year	*ATC code*	*00/01*	*01/02*	*02/03*	*03/04*	*04/05*	*05/06*	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*20/21*
Butyrophenones																						
Haloperidol	N05AD01	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Benperidol	N05AD07	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O					
Broomperidol	N05AD07	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Droperidol	N06AD08	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Melperon	N05AD04				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Pipamperone	N05AD05	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Phenothiazines																						
Chlorpromazine	N05AA01	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	O
Alimemazine	R06AD01	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O					
Flufenazine	N05AB02	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Levomepromazine	N05AA02				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Perazine	N05AB10	B	B	B																		
Perphenazine	N05AB03	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Periciazine	N05AC01	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Pipotiazine	N05AC04	B	B	B	B	B	B															
Promazine	N05AA03	B	B	B	B	B	B	B	B													
Prothipendyl	N05AX07			B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Thioriazine	N05AB08	B	B	B	B	B	B	B	B													
Thioproperazine	N05AB08			B	B	B	B															
Trifluoperazine	N05AB06	B	B	B	B	B	B															
Triflupromazine	N05AA05	B	B	B	B	B	B															
Thioxanthenes																						
Chloorprotixeen	N05AF03	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Flupentixol	N05AF01	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Zuclopentixol	N05AF05	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Tiotixene	N05AF04	B1	B1	B1																		
Butylamines																						
Fluspirilene	N05AG01	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Penfluridol	N05AG03	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Pimozide	N05AG02	B1	B1	B1	B1	B1	B1	B1	B1	O	O	O	O	O	O	O	O	O	O	O	O	O
Atypical																						
Amisulpride	N05AL05				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Asenapine	N05AH05													O	O	O	O	O	O	O	O	O
Aripiprazol	N05AX12						B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
Brexpiprazol	N05AX16																					O
Cariprazine	N05AX15																				O	O
Clozapine	N05AH02	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Levosulpiride	N05AL07				B	B	B	B	B	O	O											
Lurasidone	N05AE05																	O	O	O	O	O
Olanzapine	N05AH03	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
Paliperidone	N05AX13									O	O	O	O	O	O	O	O	O	O	O	O	O
Quetiapine	N05AH04			B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
Risperidone	N05AX08	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Sertindole	N05AE03					B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Sulpride	N05AL01	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Sultopride	N05AL02				B	B	B	B	B	O	O											
Other																						
Clotiapine	N05AH06				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Tiapride	N05AL03	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Veralipride	N05AL06				B	B	B	B	B													
lithium	N05AN01				D	D	D	D	D	T	T	T	T	T	T	T	T	T	T	T	T	RA

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Antidepressants

Antidepressants *year*	*ATC code*	*00/01*	*01/02*	*02/03*	*03/04*	*04/05*	*05/06*	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*20/21*
TCA's																						
Amitriptyline	N06AA09	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Clomipramine	N06AA04	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Imipramine	N06AA02	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Nortriptyline	N06AA10	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Desipramine	N06AA01	B	B	B	B	B	B															
Dosulepin	N06AA16	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Doxepin	N06AA12	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Maprotiline	N06AA21	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Melitracen	N06AA14					B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Opipramol	N06AA05	B	B	B																		
Trimipramine	N06AA06	B	B	B	B	B	B															
SSRI's																						
Citalopram	N06AB04			B	B	B	B	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Fluoxetine	N06AB03	C	C	C	C	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Paroxetine	N06AB05	B	B	B	B	C	C	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Sertraline	N06AB06	B	B	B	B	B	B	C	C	F	F	F	F	F	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Escitalopram	N06AB10						B	B	B	O	O	O	O	O	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Fluvoxamine	N06AB08	B1	B1	B1	B1	B1	B1	B1	B1	O	O	O	O	O	F	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Nefazodone	N06AX06			B	B																	
Other																						
Agomelatine	N06AX22											O	O	O	O	O	O	O	O	O	O	O
Bupropion	N06AX12							B1	B1	O	O	O	O	O	O	F	F	F	F	F	F	WV (1e/2e) MR (3e)
Duloxetine	N06AX21							B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
Phenelzine	N06AF03				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Mianserin	N06AX03	B1	B1	B1	B1	B1	B1	B1	B1	O	O	O	O	O	O	O	O	O	O	O	O	O
Mirtazapine	N06AX11	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	MR (3e)
Moclobemide	N06AG02	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Melitracen	N06CA02				B	B	B	B														
Reboxetine	N06AX18				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
St. John's Wort	N06AX25				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Tranylcypromine										O	O	O	O	O	O	O	O	O	O	O	O	O
Vortioxetine	N06AX26																O	O	O	O	O	O
Trazodone	N06AX05	B	B	B	B	B	B	B	B	O	O	O	O	O	O	F	F	F	F	F	F	O (1e/2e) MR (3e)
Venlafaxine	N06AX16	B	B	B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e/2e) MR (3e)
Viloxazine	N06AX09				B																	
Lithium	N05AN01	D	D	D																		

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Psychostimulantia

Psychostimulantia																						
year	*ATC code*	*00/01*	*01/02*	*02/03*	*03/04*	*04/05*	*05/06*	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*20/21*
Atomoxetine	N06BA09							B3	B3	O	O	O	O	O	O	O	O	O	O	O	O	O
Dexamfetamine	N06BA02															O	O	O	O	O	O	MR
Fenetylline	N06BA10				B	B	B	B	B	O	O											
Hydroxyboterzuur	N01AX11									O	O	O	O	O	O	O	O	O	O	O	O	
Guanfacine	C02AC02																					O
Lisdexamfetamine	N06BA12																					O
Methylphenidate	N06BA04			B2	B2	B2	B2	B2	B2	O	O	O	O	O	O	O	O	O	O	O	O	WV (1e) MR (2e/3e)
Modafinil	N06BA07				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	TN	RA
Sodium oxybate	N07XX04															O	O	O	O	O	O	O
Pitolisant	N07XX11																		O	O	O	O

F=farmacologisch effect, controle bij gebruik. O=onvoldoende ervaring, risico onbekend. R=ruime ervaring, kan gebruikt worden. T=teratogeen effect, controle bij gebruik. WO=waarschijnlijk veilig onder voorwaarden. MR=mogelijk risico. WV=waarschijnlijk veilig. RA=risico op aangeboren afwijking. TN=teratogeen effect, (tijdelijk) niet gebruiken. FN=farmacologisch effect, (tijdelijk) niet gebruiken. A/B(1,2,3)/C/D=Health Base classification 1999-2008.

Antivertigo

Antivertigo																						
year	*ATC code*	*00/01*	*01/02*	*02/03*	*03/04*	*04/05*	*05/06*	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*20/21*
Betahistine	N07CA01				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Cinnarizine	N07CA02	B2	B2	B2	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Flunarizine	N07CA03				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Piracetam	N07BX03				B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O

F=farmacologisch effect, controle bij gebruik. O=onvoldoende ervaring, risico onbekend. R=ruime ervaring, kan gebruikt worden. T=teratogeen effect, controle bij gebruik. WO=waarschijnlijk veilig onder voorwaarden. MR=mogelijk risico. WV=waarschijnlijk veilig. RA=risico op aangeboren afwijking. TN=teratogeen effect, (tijdelijk) niet gebruiken. FN=farmacologisch effect, (tijdelijk) niet gebruiken. A/B(1,2,3)/C/D=Health Base classification 1999-2008.

Parasympolytica

Parasympolytica																						
year	*ATC code*	*00/01*	*01/02*	*02/03*	*03/04*	*04/05*	*05/06*	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*20/21*
Atropine	A03BA01	A	A	A	A	A	A	C	C	FN	FN											
Aclidinium	RO3BB05														O	O	O	O	O	O	O	O
Papaverine	A03AD01	A	A	A	A	A	A	B	B													
Mebeverine	A03AA04	B	B	B	B	B	B	B	B	O	O											
Butylscopolamine	A03BB01	B2	B2	B2	B2	B2	B2	B2	B2	O	O											
Glycopyrronium	A03AB02	B2	B2	B2	B2	B2	B2	B2	B2							O	O	O	O	O	O	O
Hyoscyamine	A03BA03	B2	B2	B2	B2	B2	B2															
Propantheline	A03AB05	B2	B2	B2	B2	B2	B2	B2	B2													
Ipratropium	R01AX03	B1	B1	B1	B1	B1	B1	B1	B1	O	O	O	O	O	O	O	O	O	O	O	O	O
Tiotropium	RO3BB04			B	B	B	B	B	B	O	O	O	O	O	O	O	O	O	O	O	O	O
Umeclidinium	R03BB07																O	O	O	O	O	O

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Anti-addictives

Anti-addictives																						
year	*ATC code*	*00/01*	*01/02*	*02/03*	*03/04*	*04/05*	*05/06*	*06/07*	*07/08*	*08/09*	*09/10*	*10/11*	*11/12*	*12/13*	*13/14*	*14/15*	*15/16*	*16/17*	*17/18*	*18/19*	*19/20*	*20/21*
Nicotine	N07BA01	D	D	D	D	D	D	D	D	T	T	TN	TN	TN	TN	TN	TN	TN	TN	TN	TN	MR
Acamprosate	N07BB03			B1	B1	B1	B1	B1	B1	O	O	O	O	O	O	O	O	O	O	O	O	O
Bupropion	N06AX12			B2	B2	B2	B2	B2	B2	O	O	O	O	O	O	F	F	F	F	F	F	WV (1e) MR (2e/3e)
Calciumcarbimide	N07BB02	B2	B2	B2																		
Disulfiram	N07BB01	B3	B3	B3	B3	B3	B3	B3	B3	O	O	O	O	O	O	O	O	O	O	O	O	O
Nalmefene	N07BB05														O	O	O	O	O	O	O	O
Naltrexone	N07BB04				B1	B1	B1	B1	B1	O	O	O	O	O	O	O	O	O	O	O	O	O
Varenicline	N07BA03									O	O	O	O	O	O	O	O	O	O	O	O	WV

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Appendix 3: Overview of introduction and withdrawal of drugs per year from the CM

Introduced psychotropic drugs in the CM between 2000-2021

Table 15: Overview of introduced drugs per year between 2000-2021 including drug name, ATC code, pharmacological class and assigned safety classification in the CM.

Year	Drug	ATC	Pharmacological class	Safety classification
2000/2001				
2001/2002				
2002/2003	Zaleplon	N05CF03	Hypnotics, sedatives and anxiolytics/Benzodiazepines	B
	Prothipendyl	N05AX07	Antipsychotics/Phenothiazines	B
	Thioproperazine	N05AB08	Antipsychotics/Phenothiazines	B
	Quetiapine	N05AH04	Antipsychotics/Atypical	B
	Citalopram	N06AB04	Antidepressants/SSRIs	B
	Nefazodone	N06AX06	Antidepressants/SSRIs	B
	Methylphenidate	N06BA04	Psychostimulants	B2
	Acamprosate	N07BB03	Antiaddictives	B1
	Bupropion	N06AX12	Antiaddictives	B2
2003/2004	Clotiazepam	N05BA21	Hypnotics, sedatives and anxiolytics/Benzodiazepines	B
	Cloxazolam	N05BA22	Hypnotics, sedatives and anxiolytics/Benzodiazepines	B
	Ethyllofazepate	N05BA18	Hypnotics, sedatives and anxiolytics/Benzodiazepines	B
	Chloral hydrate	N05CC01	Hypnotics, sedatives and anxiolytics/Other	B
	Meprobamate	N05BC01	Hypnotics and sedatives/Other	B
	Melperon	N05AD04	Antipsychotics/Butyrophenones Antipsychotics/Phenothiazines Antipsychotics/Atypical	B
	Levomepromazine	N05AA02	Antipsychotics/Other	B
	Amisulpride	N05AL05	Antipsychotics/Atypical	
	Levosulpride	N05AL07	Antipsychotics/Atypical	B
	Sultopride	N05AL02	Antipsychotics/Atypical	B
	Veralipride	N05AN01	Antipsychotics/Other	B
	Lithium	N05AN01	Antidepressants/Other	D
	Phenelzine	N06AF03	Antidepressants/Other	B
	Melitracen	N06CA02	Antidepressants/Other	B
	Reboxetine	N06AX18	Antidepressants/Other	B
	St. John's Wort	N06AX25	Antidepressants/Other	B
	Viloxazine	N06AX09	Psychostimulants	B
	Fenethylline	N06BA10	Psychostimulants	B
	Modafinil	N06BA07	Antivertigo	B
	Betahistine	N07CA01	Antivertigo	B
	Flunarizine	N07CA03	Antivertigo	B

	Piracetam Naltrexone	N07BX03 N07BB04	Anti-addictives	B B1
2004/2005	Sertindole	N05AE03	Antipsychotics/Atypical	B
2005/2006	Aripiprazole Escitalopram	N05AX12 N06AB10	Antipsychotics/Atypical Antidepressants/SSRIs	B B
2006/2007	Bupropion Duloxetine Atomoxetine	N06AX12 N06AX21 N06BA09	Antidepressants/Other Antidepressants/Other Psychostimulants	B1 B B3
2007/2008				
2008/2009	Melatonin Paliperidone Tranylcypromine Varenicline	N05CH01 N05AX13 N06AF04 N07BA03	Hypnotics, sedatives and anxiolytics/Other Antipsychotics/Atypical Antidepressants/Other Anti-addictives	O O O O
2009/2010				
2010/2011				
2011/2012				
2012/2013	Asenapine	N05AH05	Antipsychotics/Atypical	O
2013/2014				
2014/2015	Dexamphetamine Sodium oxybate	N06BA02 N07XX04	Psychostimulants Psychostimulants	O O
2015/2016	Vortioxetine	N06AX26	Antidepressants/Other	O
2016/2017	Lurasidone	N05AE05	Antipsychotics/Atypical	O
2017/2018	Pitolisant	N07XX11	Psychostimulants	O
2018/2019				
2019/2020	Cariprazine	N05AX15	Antipsychotics/Atypical	O
2020/2021	Brexpiprazol Lisdexamfetamine	N05AX15 N06BA12	Antipsychotics/Atypical Psychostimulants	O O

Withdrawn psychotropic drugs in the CM between 2000-2021

Table 16: Overview of withdrawn drugs per year from the CM between 2000-2021 including drug name, ATC code, pharmacological class and last assigned safety classification.

Year	***Drug***	***ATC***	***Pharmacological class***	***Risk classification***
2000/2001				
2001/2002				
2002/2003	Tiotixene Opipramol Lithium Calciumcarbimide	N05AF04 N06AA05 N05AN01 N07BB02	Antipsychotics/Thioxanthenes Antidepressants/ TCAs Antidepressants/Other Anti-addictives	B1 B D B2
2003/2004	Nefozadone Viloxazine	NO6AX21 N06AX09	Antidepressants/SSRIs Antidepressants/Other	B B
2004/2005				
2005/2006	Medazepam	N05BA03	Hypnotics, sedatives and anxiolytics/Benzodiazepines	B

	Pipotiazine	N05AC04	Antipsychotics/Phenothiazines	B
	Thioproperazine	N05AB08	Antipsychotics/Phenothiazines	B
	Trifluoperazine	N05AB06	Antipsychotics/Phenothiazines	B
	Triflupromazine	N05AA06	Antipsychotics/Phenothiazines	B
	Trimipramine	N06AA06	Antidepressants/TCAs	B
2006/2007	Melitracen	N06CA02	Antidepressants/Other	B
2007/2008	Ketazolam	N05BA10	Hypnotics, sedatives and anxiolytics/Benzodiazepines	B
	Promazine	N05AA03	Antipsychotics/Phenothiazines	B
	Thioridazine	N05AC02	Antipsychotics/Phenothiazines	B
	Veralipride	N05AL06	Antipsychotics/Other	B
2008/2009				
2009/2010	Levosulpride	N05AL07	Antipsychotics/Atypical	O
	Sultopride	N05AL02	Antipsychotics/Atypical	O
	Fenethylline	N06BA10	Psychostimulants	O
2010/2011				
2011/2012				
2012/2013				
2013/2014	Zaleplon	N05CF03	Hypnotics, sedatives and anxiolytics/Benzodiazepines	O
2014/2015				
2015/2016	Meprobamate	N05BC01	Hypnotics, sedatives and anxiolytics/Other	O
	Benperidol	N05AD07	Antipsychotics/Butyrophenones	O
2016/2017				
2017/2018				
2018/2019				
2019/2020	Chlordiazepoxide	N05BA02	Hypnotics, sedatives and anxiolytics/Other	O
	Cloxazolam	N05BA22	Hypnotics, sedatives and anxiolytics/Other	O
	Hydroxyzine	N05BB01	Hypnotics, sedatives and anxiolytics/Other	O
2020/2021				