Benefit assessment of bupropion, cytisine, nicotine and varenicline for smoking cessation in severe tobacco dependence[1]

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

This report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed Form for disclosure of potential conflicts of interest from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A9 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

- Sabrina Kastaun, University Hospital Düsseldorf, Institute for General Medicine (ifam), Centre for Health and Society (chs), Düsseldorf, Germany

IQWiG thanks the external experts for their collaboration in the project.

Patient and family involvement

Patients or family members were consulted during the preparation of the report.

Two people affected participated in the discussion. Its aim was to obtain information on the following topics: The impact of the condition on life and daily activities and how people cope, treatment preferences including treatment goals, and experiences and concerns about treatment.

IQWiG would like to thank the participants for taking part in the discussion. They were not involved in the actual writing of the report.

IQWiG employees

- Claudia Selbach
- Christian Siebel
- Ulrich Grouven
- Marco Knelangen
- Petra Kohlepp
- Philip Kranz
- Jona Lilienthal
- Sabine Ostlender
- Daniela Preukschat

Keywords

Bupropion, Cytisine, Nicotine, Varenicline, Smoking, Benefit Assessment, Systematic Review

Key statement

Research question

The objective of this investigation is to assess the benefit of bupropion, cytisine, nicotine, and varenicline, also in combination with each other, for smoking cessation in comparison with no drug treatment in smokers with severe tobacco dependence regarding patient-relevant outcomes.

Depending on the interventions to be evaluated and their combinations, the following research questions also arise from the respective Summaries of Product Characteristics (SPCs):

Table: Research questions of the benefit assessment

Research question	Therapeutic indication	Intervention	Comparator intervention
1	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Bupropion	No drug treatment for smoking cessation[b]
2	Smokers aged ≥ 18 and ≤ 65 years[a] with severe tobacco dependence	Cytisine	
3	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Varenicline	
4	Smokers aged ≥ 12 years[a] with severe tobacco dependence	Nicotine[c]	
5	Smokers[d] with severe tobacco dependence	Various combinations of the drugs bupropion, cytisine, varenicline and nicotine	

a. The age of the population of smokers to be considered is determined by the approval of the respective drugs.
b. This also includes the use of placebo in the context of placebo-controlled studies. If supportive measures or non-pharmacological methods (e.g. behavioural therapeutic interventions) were used in a study for smoking cessation, it is assumed that these are carried out equally among smokers in the intervention arm and those in the comparator arm.
c. Nicotine is authorised in various forms of administration. Not all forms of nicotine administration are authorised for adolescents aged ≥ 12 and < 18 years. Nicotine is the only approved drug that can also be used in pregnant women.
d. The inclusion criterion for the age of smokers is determined by the respective combinations of drugs, taking into account the respective approvals.

Conclusion

For research question 1 on comparing bupropion to no drug therapy, 51 potentially relevant studies were identified. For research question 5, 5 relevant studies and 1 potentially relevant study were identified, each of which investigated bupropion in combination with nicotine or varenicline. Research questions 1 and 5 could not be finalised because the requested study documents for bupropion were not provided by the manufacturer. The necessary data could not be obtained through information retrieval from other sources. In addition, due to the

manufacturer's failure to provide data, no subgroup analyses could be carried out with regard to the severity of tobacco dependence, so that an effect modification by the severity of tobacco dependence for the drug bupropion or combinations with bupropion in comparison with no drug treatment cannot be excluded with sufficient certainty. An assessment of bupropion (research question 1 and 5) for smokers with severe tobacco dependence is therefore not possible.

For research question 2 on cytisine, 3 relevant studies were identified. Since subgroup analyses regarding the severity of tobacco dependence are available only for the smallest of the 3 studies, an effect modification by the severity of tobacco dependence for the drug cytisine cannot be excluded with sufficient certainty. A benefit conclusion for comparing cytisine to no drug treatment for smoking cessation for smokers with severe tobacco dependence is not possible based on the overall population of the studies in the present data situation. To enable this assessment, subgroup analyses on the characteristic of severity of tobacco dependence for the outcome "freedom from smoking" must be presented for all 3 studies.

To answer research question 3 on varenicline, a total of 20 studies were analysed on the basis of the total population after sufficiently reliable exclusion of effect modification by the characteristic of severity of tobacco dependence. For the outcome of permanent freedom from smoking, based on the available data, both at month 6 and at month 12, there is proof of a greater benefit of varenicline in comparison with no drug treatment for smoking cessation. For the outcomes “neuropsychiatric side effects”, “fatigue”, and “nausea”, there are indications of greater harm from varenicline in comparison with no drug treatment for smoking cessation. For each of the outcomes “discontinuation due to adverse events”, “dry mouth”, and “headaches”, there is also a hint of greater harm from varenicline. For all other outcomes, there are no statistically significant differences between the treatment groups or there are no (suitable) data available. It should be noted that the results on outcomes in the category of side effects and mortality are subject to uncertainty due to the lack of subgroup analyses according to Fagerström Test for Cigarette Dependence (FTCD) cut-off values, which means that it remains unclear whether there are potentially other or further advantages or disadvantages for smokers with severe tobacco dependence. It should also be noted that particularly the analysis of neuropsychiatric side effects (e.g. sleep disorders, abnormal dreams, irritability) could potentially also take withdrawal symptoms into account. In addition, adverse events were only recorded in the studies until shortly after the end of treatment. Overall, the disadvantages for individual outcomes in the side effects category and the uncertainties described do not call into question the benefit of varenicline for smokers with severe tobacco dependence, which is based on clear advantages in the key outcome of permanent freedom from smoking. In the overall assessment, there is proof of a greater benefit from varenicline in comparison with no drug treatment for smoking cessation.

A total of 43 studies were analysed to answer research question 4 on nicotine. From studies that have included pregnant smokers or adolescent smokers, no data on the outcome of permanent freedom from smoking in an operationalization suitable for benefit assessment are available. These studies were therefore not considered further in the analyses for the present benefit assessment. However, taking into account high-quality systematic reviews on these patient populations, it can be assumed that the results of the present benefit assessment are also transferable to these subpopulations. The benefit conclusion therefore refers to the entire population covered by the approval. An effect modification by the characteristic of severity of tobacco dependence can be excluded with sufficient certainty for nicotine. Based on the available data, the outcome for permanent freedom from smoking at month 6 provides proof of a greater benefit from nicotine, and for permanent freedom from smoking at month 12, there is a hint of a greater benefit from nicotine compared to no drug treatment for smoking cessation. For the present benefit assessment, permanent freedom from smoking at month 6 is considered decisive. On the other hand, for the outcomes “discontinuation due to adverse events”, “headache”, “nausea”, and “irritation of the mouth and throat”, there are indications of greater harm from nicotine in comparison with no drug therapy for tobacco cessation. Furthermore, the outcome “itching” provides a hint of greater harm from nicotine. For all other outcomes, there are no statistically significant differences between the treatment groups or there are no (suitable) data available. It should be noted that the results on outcomes in the category of side effects and mortality are subject to uncertainty due to the lack of subgroup analyses according to FTCD cut-off values, which means that it remains unclear whether there are potentially other or further advantages or disadvantages for smokers with severe tobacco dependence. The advantage of nicotine, which is shown for the decisive outcome of permanent freedom from smoking, is not called into question by the disadvantages in the outcome of discontinuation due to adverse events and the disadvantages of individual specific adverse events. This assessment remains valid despite the higher uncertainty regarding the results for the outcomes for which no subgroup analyses are available according to FTCD cut-off values, particularly due to the significant advantage in the relevant outcome of permanent freedom from smoking. In the overall assessment, there is proof of a greater benefit from nicotine in comparison with no drug treatment for smoking cessation.

The following table summarises the results of the benefit assessment of bupropion, cytisine, nicotine and varenicline for smoking cessation in severe tobacco dependence.

Table: Conclusion of the benefit assessment

Research question	Therapeutic indication	Intervention	Comparator intervention	Conclusion
1	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Bupropion	No drug treatment for smoking cessation[b]	No conclusion possible
2	Smokers aged ≥ 18 and ≤ 65 years[a] with severe tobacco dependence	Cytisine		No conclusion possible
3	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Varenicline		Proof of greater benefit of varenicline versus the comparator intervention
4	Smokers aged ≥ 12 years[a] with severe tobacco dependence	Nicotine[c]		Proof of greater benefit of nicotine versus the comparator intervention
5	Smokers[d] with severe tobacco dependence	Various combinations of the drugs bupropion, cytisine, varenicline and nicotine		No conclusion possible

a. The age of the population of smokers to be considered is determined by the approval of the respective drugs.
b. This also includes the use of placebo in the context of placebo-controlled studies. If supportive measures or non-pharmacological methods (e.g. behavioural therapeutic interventions) were used in a study for smoking cessation, it is assumed that these are carried out equally among smokers in the intervention arm and those in the comparator arm.
c. Nicotine is authorised in various forms of administration. Not all forms of nicotine administration are authorised for adolescents aged ≥ 12 and < 18 years. Nicotine is the only approved drug that can also be used in pregnant women.
d. The inclusion criterion for the age of smokers is determined by the respective combinations of drugs, taking into account the respective approvals.

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List of abbreviations

Abbreviation	Meaning
AEs	adverse events
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	clinical study report
FTCD	Fagerström Test for Cigarette Dependence
FTND	Fagerström Test for Nicotine Dependence
FTQ	Fagerström Tolerance Questionnaire
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IITs	investigator-initiated studies
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MACE	adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
nAChRs	nicotinic acetylcholine receptors
RCTs	randomized controlled trials
SAEs	serious adverse events
SCQoL	Smoking Cessation Quality of Life
SF-36	Short Form-36 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

Smoking and tobacco dependence – epidemiology and consequences

Tobacco smoking is considered the most widespread avoidable health risk in Germany. While the proportion of smokers has been slightly declining since the 1980s [1], according to the Microcensus data from 2017, a proportion of 22.4% of the total population aged 15 and over still smoked in Germany. The proportion of smokers was 19% for women and 26% for men [2,3]. In the German survey on smoking behaviour (DEBRA study) conducted in March 2023, a significantly higher prevalence of 32.4% was recorded among individuals aged 14 and older [4]. Smoking is often started in adolescence or as a young adult: According to the Microcensus, the average age of people starting to smoke was 15 to 20 years depending on the sex and current age of the respondents [2]. The term “tobacco dependence” is used both in the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) and in the literature in connection with the description of dependent smoking.

Smoking can have far-reaching health consequences. On the one hand, tobacco smoke, which contains more than 90 certain or suspected mutagenic or carcinogenic substances [5], can damage almost all organs of the body. Around 80% of all lung cancer cases are attributable to smoking. Smoking is also the most significant cause of chronic obstructive pulmonary disease. In addition, smokers have more than twice the risk of cardiovascular diseases and twice the risk of stroke compared to non-smokers [6]. In 2018, for example, around 127 000 people in Germany died from the health consequences of smoking [6].

Furthermore, tobacco smoke contains the primarily psychotropic substance nicotine. Nicotine is the key substance for the development and maintenance of tobacco dependence. The binding of nicotine to nicotinic acetylcholine receptors (nAChRs), particularly in the brain, releases messenger substances such as dopamine, which trigger a feeling of well-being. Repeated consumption of nicotine increases the production of nAChRs in the brain. If there is not enough nicotine available to bind to the existing nAChRs, strong withdrawal symptoms can occur due to a reduced release of neurotransmitters such as dopamine, which in turn can lead to compulsive consumption [6].

Aside from the risks of secondary illnesses and the development of tobacco dependence in the smoking individual, the illnesses caused by smoking also lead to annual costs of approximately €30 billion for the German healthcare system. In addition, there are further indirect social costs (e.g. due to productivity losses or loss of resources) of around €67 billion per year [6,7].

Tobacco dependence and severity classification

Tobacco consumption is self-harming behaviour and does not initially constitute a disorder [3]. However, repeated consumption can lead to the disorder "tobacco dependence". Tobacco

dependence is a mental and psychological dependence. In the latter case, the learning of smoking behaviour takes place in the brain via messenger substances. As part of a conditioning process, smoking behaviour is continuously associated with certain situations and sensations [6]. In the literature, the terms nicotine dependence, tobacco dependence, or cigarette dependence are used [8]. However, narrowing down the term to nicotine dependence does not adequately reflect the special features of dependent smoking: nicotine as a single substance without the other accompanying substances in tobacco smoke and in a different pharmacokinetic formulation than in cigarettes has a lower reinforcing effect and a lower dependence potential than tobacco smoking. The substance that primarily causes dependence is therefore nicotine, but tobacco dependence refers to smoking in the form of tobacco, e.g. a cigarette [3]. In Germany, tobacco dependence is coded using the diagnosis code F17.2 according to ICD-10. This code includes mental and behavioural disorders due to tobacco use that have led to a dependence syndrome. A dependence syndrome for mental and behavioural disorders, including tobacco dependence, is diagnosed if at least 3 of the following 6 criteria are met repeatedly within a 1-year period or continuously during a 1-month period [3,9]:

- There is a strong desire to take the substance.
- There are difficulties in controlling consumption.
- Despite harmful consequences, there is persistent substance use.
- Substance use is prioritised over other activities and obligations.
- An increase in tolerance develops.
- A physical withdrawal syndrome arises.

To assess the severity of dependence, the Fagerström Test for Cigarette Dependence (FTCD; alternative name Fagerström Test for Nicotine Dependence [FTND] revision of the original Fagerström Tolerance Questionnaire [FTQ] [10]) is available in particular, which is also recommended for this purpose in the current S3 guideline "Smoking and Tobacco Dependence: Screening, Diagnosis and Treatment" [3]. According to the sample anamnesis form proposed in the S3 guideline, there is a strong dependence when a score of 8 or more points is reached in the Fagerström Test, with the value range of 6 to 7 points being referred to as "moderate to strong dependence". In international publications, a threshold of 6 or more points is often used to define severe tobacco dependence [11-14]. There are no validated instruments for the differentiation of severe tobacco dependence in adolescent smokers.

Treatment options for tobacco dependence

The primary goal of treating tobacco dependence is to achieve complete or permanent freedom from smoking [3,5,15]. If smokers are unable to quit smoking permanently solely by

their own volition, which around 3% to 5% of smokers manage to do [16], various treatment options are available to achieve permanent freedom from smoking, such as behavioural therapy interventions (including e.g. motivational measures) and drug therapies are available [3]. At the time of commissioning by the Federal Joint Committee (G-BA), the drugs bupropion, cytisine, nicotine, and varenicline were approved for the pharmacological treatment of tobacco dependence in Germany.

Bupropion belongs to the pharmacotherapeutic class of antidepressants and selectively inhibits the reuptake of noradrenaline and dopamine in particular. The exact mechanism by which bupropion helps individuals to remain abstinent from smoking is unknown [17]. However, it is assumed that the inhibition of noradrenaline and dopamine reuptake also counteracts the occurrence of withdrawal symptoms and the urge to smoke [18]. The drugs cytisine and varenicline are partial nAChR agonists. They compete with nicotine for the same binding site on nAChRs, thereby reducing withdrawal symptoms and the urge to smoke, while at the same time reducing the rewarding effect of the smoked cigarette due to the lower binding of nicotine [15,18-20]. Temporarily replacing the nicotine that would have been supplied by smoking tobacco with nicotine as a medication reduces withdrawal symptoms and the urge to smoke [15,18].

Various systematic reviews, such as Fanshawe 2017, Hartmann-Boyce 2018, Claire 2020, Thomas 2021, Hajizadeh 2023 and Livingstone-Banks 2023 [21-26], have already investigated how the use of various medications to treat tobacco dependence in smokers affects the outcomes of permanent freedom from smoking and side effects in particular. In these overview studies, each of the different drugs showed an advantage in comparison with placebo or no drug treatment in terms of permanent freedom from smoking.

However, no summary results on the benefits and harms of the drugs bupropion, cytisine, nicotine, and varenicline in the group of smokers with severe tobacco dependence exist so far.

2 Research question

The objective of this investigation is to

- assess the benefit of bupropion, cytisine, nicotine, and varenicline, also in combination with each other, for smoking cessation in comparison with no drug treatment

in smokers with severe tobacco dependence regarding patient-relevant outcomes.

Depending on the interventions to be evaluated and their combinations, the following research questions also arise from the respective Summaries of Product Characteristics (SPCs):

Table 1: Research questions of the benefit assessment

Research question	Therapeutic indication	Intervention	Comparator intervention
1	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Bupropion	No drug treatment for smoking cessation[b]
2	Smokers aged ≥ 18 and ≤ 65 years[a] with severe tobacco dependence	Cytisine	
3	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Varenicline	
4	Smokers aged ≥ 12 years[a] with severe tobacco dependence	Nicotine[c]	
5	Smokers[d] with severe tobacco dependence	Various combinations of the drugs bupropion, cytisine, varenicline and nicotine	

a. The age of the population of smokers to be considered is determined by the approval of the respective drugs.
b. This also includes the use of placebo in the context of placebo-controlled studies. If supportive measures or non-pharmacological methods (e.g. behavioural therapeutic interventions) were used in a study for smoking cessation, it is assumed that these are carried out equally among smokers in the intervention arm and those in the comparator arm.
c. Nicotine is authorised in various forms of administration. Not all forms of nicotine administration are authorised for adolescents aged ≥ 12 and < 18 years. Nicotine is the only approved drug that can also be used in pregnant women.
d. The inclusion criterion for the age of smokers is determined by the respective combinations of drugs, taking into account the respective approvals.

3 Methods

The target population of the benefit assessment consisted of smokers with severe tobacco dependence. In the benefit assessment, the conclusions on smokers with severe tobacco dependence – provided that an effect modification due to the severity of tobacco dependence can be excluded with sufficient certainty for the respective drug – are made on the basis of the total population of the included studies (see sections 4.4.1 and 4.5.1).

The test interventions consisted of bupropion, cytisine, varenicline, nicotine or combinations of these drugs in accordance with the SPCs. The comparator intervention was no drug treatment for smoking cessation.

The following patient-relevant outcomes were taken into account in the investigation:

- All-cause mortality
- Permanent freedom from smoking (at month 6 and at month 12)
- Other morbidity outcomes
- Health-related quality of life
- Overall rate of serious adverse events (SAEs)
- Overall rate of discontinuations due to adverse events (AEs)
- Cardiovascular side effects
- Neuropsychiatric side effects
- Other specific AEs
  - Dry mouth
  - Fatigue
  - Headache
  - Nausea
  - Itching
  - Rash
  - Irritations in the mouth and throat

Only randomized controlled trials (RCTs) with a minimum duration of 6 months were included in the benefit assessment.

Permanent freedom from smoking was defined as continuous freedom from smoking without exceptions (no cigarette smoked during the entire survey period) from day 1 of freedom from

smoking (different for each study; between the start of the study and week 12 of the study) up to the survey time point month 6 or month 12. With the exception of the results for research question 2 (cytisine), point-by point freedom from smoking such as during the 7 days before the survey (referred to below as 7-day point prevalence) or during the 30 days before the survey were not considered. Due to the limited data situation, the results for the 7-day point prevalence outcomes are also presented for the drug cytisine. If reported in the studies, biochemically validated results on permanent freedom from smoking are favoured in the analyses for the present benefit assessment.

To ensure the patient relevance of the outcome “cardiovascular side effects”, this was defined as major adverse cardiovascular events (MACE) or cardiovascular SAEs. For the present benefit assessment, serious adverse events (SAEs) in the System Organ Class (SOC) “cardiac disorders” were used according to the Medical Dictionary for Regulatory Activities (MedDRA) or, if other coding systems were used, a comparable operationalization. The outcome of neuropsychiatric side effects was defined as events in the SOC “psychiatric disorders”. This outcome is of minor importance for nicotine and is therefore not considered in the benefit assessment for research question 4. Due to the administration form of varenicline (film-coated tablet), the outcome of irritations in the mouth and throat (throat irritation) is not relevant for research question 3 and is therefore not considered in the benefit assessment for research question 3. For the additional specific AEs defined in the report plan, the preferred terms (PTs) dry mouth, fatigue, headache, nausea, pruritus, rash, and throat irritation were used according to MedDRA or comparable operationalizations. Analyses of AEs include all events that occurred during the observation period.

In parallel to the preparation of the report protocol, a search for systematic reviews was conducted in the MEDLINE database (which includes the Cochrane Database of Systematic Reviews) and the HTA database as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

It was ascertained whether at least 1 high-quality, current systematic review existed whose information retrieval was a suitable basis (hereinafter: basic SR).

The systematic literature search for studies was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials.

In addition, the following information sources and search techniques were taken into account: trial registries, manufacturer queries, G-BA and IQWiG websites as well as the screening of reference lists, documents made available from hearing procedures, and author queries.

Relevant studies were selected by 2 persons independently from one another. Any discrepancies were resolved by discussion between them. Data were extracted into

standardized tables. To assess the qualitative certainty of results, risk of bias criteria across outcomes and outcome-specific risk of bias criteria were assessed, and the risk of bias was rated as high or low in each case. The results of the individual studies were described according to outcomes.

In addition to the comparison of the individual studies' results, metaanalyses and sensitivity analyses were conducted and effect modifiers investigated, provided that the methodological prerequisites had been met.

For each outcome, a conclusion was drawn regarding the evidence base for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: There was either proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or none of those 3 situations. The latter was the case if no data were available or the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion "There is no hint of (greater) benefit or (greater) harm" was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

4 Results

4.1 Results of the information retrieval

No systematic reviews were considered as basic SRs for the purpose of identifying primary studies, as no systematic reviews were found that comprehensively covered all issues.

The information retrieval revealed 136 relevant RCTs for research questions 2, 3 and 4 (see Section A3.1). For research question 2 (cytisine), 3 relevant studies were identified. For research question 3 (varenicline), 38 relevant studies were identified and for research question 4 (nicotine), 100 relevant studies were identified. 5 of these studies [27-32] are relevant for both research question 3 (varenicline) and research question 4 (nicotine) (see Table 2). No relevant planned and no relevant ongoing studies were identified for questions 2, 3 and 4.

Relevant and potentially relevant studies were identified for research questions 1 (bupropion) and 5 (combinations). Only combinations with bupropion were identified for research question 5. However, the relevance of the majority of the studies could not be conclusively assessed, as the manufacturer of bupropion did not provide the requested study documents. The limited data available were not analysed (see Section 4.2).

The search strategies for bibliographic databases and trial registries are found in the appendix. The last search was conducted on 1 September 2022.

Table 2: Study pool of the benefit assessment (multipage table)

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
Research question 2 – cytisine				
Dogar 2020	Yes [33]	Yes [34]/No	No	No
Vinnikov 2008	Yes [35]	No	No	Yes [36]
West 2011	Yes [37]	Yes [38]/No	No	No
Research question 3 – varenicline				
A3051007/A3051018	Yes [39]	No	Yes [40,41]	Yes [42]
A3051028	Yes [43,44]	Yes [45]/No	Yes [46]	Yes [42]
A3051036	Yes [47,48]	Yes [49]/No	Yes [50]	Yes [42]
A3051045	Yes [51]	Yes [52]/No	Yes [53]	Yes [42]
A3051046[a]	Yes [54]	Yes [55]/No	Yes [56]	Yes [42]
A3051049	Yes [57]	Yes [58-60]/Yes [58-60]	Yes [61]	Yes [42]
A3051054	Yes [62]	Yes [63,64]/Yes [63,64]	Yes [65]	Yes [42]
A3051055	Yes [66]	No	Yes [67]	Yes [42]
A3051072[a]	Yes [68]	Yes [69]/Yes [69]	Yes [70]	Yes [42]
A3051075[a]	Yes [71]	Yes [72-74]/Yes [72-74]	Yes [75]	Yes [42]
A3051080	Yes [76]	Yes [77]/Yes [77]	Yes [78]	Yes [42]
A3051095	Yes [79]	Yes [80-82]/ Yes [80-82]	Yes [83]	Yes [42]
A3051122	Yes [84]	Yes [85-87]/Yes [85-87]	Yes [88]	Yes [42]
A3051139	Yes [89]	Yes [90-92]/Yes [90-92]	Yes [93]	Yes [42]
ANRS144 Inter-ACTIV	Yes [94]	Yes [95]/No	No	No
Ashare 2019	Yes [96]	Yes [97]/Yes [97]	No	No
Bidwell 2017[a]	Yes [98]	Yes [99]/Yes [99]	No	No
Bold 2019[a]	Yes [100]	Yes [101]/Yes [101]	No	No
CHAMPIX ASTHMA[a]	Yes [102]	Yes [103,104]/Yes [104]	No	No
Chen 2020[a]	Yes [32]	Yes [105]/Yes [105]	No	No
Chengappa 2014[a]	Yes [106]	Yes [107]/Yes [107]	No	No
Cinciripini 2013	Yes [108]	Yes [109]/Yes [109]	No	No
Cinciripini 2018	Yes [110]	Yes [111]/Yes [111]	No[b]	No
DIASMOKE	Yes [112,113]	Yes [114,115]/No	No	No
EAGLES/CATS	Yes [116-123]	Yes [124-127]/Yes [124-127]	Yes [27,28]	Yes [42]
EVITA	Yes [128-130]	Yes [131]/Yes [131]	No	No
Heydari 2012[a]	Yes [29]	Yes [132]/No	No	No
Hughes 2011[a]	Yes [133]	Yes [134]/Yes [134]	No	No
Hurt 2018[a]	Yes [135]	Yes [136]/yes [136]	No	No

Table 2: Study pool of the benefit assessment (multipage table)

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
KIS-IV[a]	Yes [137]	Yes [138]/Yes [138]	No	No
Lerman 2015[a]	Yes [30,139]	Yes [140]/Yes [140]	No	No
Nahvi 2014[a]	Yes [141]	Yes [142]/Yes [142]	No	No
Niaura 2008	Yes [143]	No	No	No
SAVE[a]	Yes [144]	Yes [145]/No	No	No
Stein 2013	Yes [31]	Yes [146]/Yes [146]	No	No
Steinberg 2011[a]	Yes [147]	No	No	No
STOP[a]	Yes [148-150]}	Yes [151]/No	No	No
Wong 2012[a]	Yes [152]	No	No	No
Research question 4 – nicotine				
94NNBT011	No	No	Yes [153]	Yes [154]
94NNBT012	No	No	Yes [155]	Yes [154]
96-NNCG-008[a]	No	No	Yes [156]	No
96-NNIN-016	No	No	Yes [157]	Yes [154]
97-NITG-001[a]	Yes [158]	Yes [159]/No	Yes [160]	Yes [154]
980-CHC-1013-028	Yes [161]	No	Yes [162]	Yes [154]
980-CHC-9021-013	No	No	Yes [163]	Yes [154]
98-NNCG-014	Yes [164]	No	Yes [165]	Yes [154]
98-NNCG-017	No	No	Yes [166]	Yes [154]
98-NNIN-027	No	No	Yes [167]	Yes [154]
A534252[a]	Yes [168]	Yes [169]/No	No	No
A6431111	No	Yes [170-172]/Yes [171,172]	Yes [173]	Yes [154]
Abdelghany 2022	Yes [174]	Yes [175]/Yes [175]	No	No
Areechon 1988[a]	Yes [176]	No	No	No
Bock 2010[a]	Yes [177]	No	No	No
Bolliger 2000	Yes [178,179]	No	No	No
Campbell 1991[a]	Yes [180]	No	No	No
Chan 2011[a]	Yes [181]	No	No	No
Chen 2020[a]	Yes [32]	Yes [105]/Yes [105]	No	No
CHN-Nicotine Mint Lozenge-002	Yes [182]	Yes [183]/Yes [183]	Yes [184]	Yes [185]
Cinciripini 1996[a]	Yes [186]	No	No	No
Cooper 2005[a]	Yes [187]	No	No	No
Cummins 2016[a]	Yes [188]	No	No	No

Table 2: Study pool of the benefit assessment (multipage table)

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
Daughton 1998	Yes [189]	No	No	No
EAGLES/CATS	Yes [116-123]	Yes [124-127]/Yes [124-127]	Yes [27,28]	Yes [42]
El-Mohandes 2013[a]	Yes [190]	Yes [191]/No	No	No
Etter 2002[a]	Yes [192-194]	No	No	No
Fagerstrom 1982[a]	Yes [195]	No	No	No
Fee 1982[a]	Yes [196]	No	No	No
Fiore 1994[a]	Yes [197]	No	No	No
Fortmann 1995[a]	Yes [198]	No	No	No
Gallagher 2007[a]	Yes [199]	No	No	No
Garvey 2000	Yes [200]	No	No	No
Gepner 2011 / Piper 2009[a]	Yes [201,202]	Yes [203]/Yes [203]	No	No
Gilbert 1989[a]	Yes [204]	No	No	No
Gourlay 1995	Yes [205]	No	No	No
Hall 1985[a]	Yes [206]	No	No	No
Hall 1987[a]	Yes [207]	No	No	No
Harackiewicz 1988	Yes [208]	No	No	No
Heydari 2012[a]	Yes [29]	Yes [132]/No	No	No
Hill 1993[a]	Yes [209]	No	No	No
Hjalmarson 1984	Yes [210]	No	No	No
Hollis 2007[a]	Yes [211]	No	No	No
Hotham 2006[a]	Yes [212]	No	No	No
Huber 1988[a]	Yes [213]	No	No	No
Huber 2003[a]	Yes [214]	No	No	No
Hughes 1989	Yes [215]	No	No	No
Hughes 1990	Yes [216]	No	No	No
Hughes 1991[a]	Yes [217,218]	No	No	No
Hughes 1999[a]	Yes [219]	No	No	No
Hughes 2003	Yes [220]	No	No	No
Hurt 1994[a]	Yes [221]	No	No	No
Jamrozik 1984[a]	Yes [222]	No	No	No
Jensen 1990	Yes [223]	No	No	No
Jorenby 1999	Yes [224,225]	No	No	No
Joseph 1996	Yes [226]	No	No	No
Joyce 2008[a]	Yes [227]	No	No	No

Table 2: Study pool of the benefit assessment (multipage table)

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
Killen 1990[a]	Yes [228,229]	No	No	No
Killen 1997[a]	Yes [230]	No	No	No
Kinnunen 2008[a]	Yes [231]	No	No	No
Lerman 2015[a]	Yes [30]	Yes [140]/Yes [140]	No	No
Malhotra 2022[a]	Yes [232]	No	No	No
McGovern 1992[a]	Yes [233]	No	No	No
Moolchan 2005[a]	Yes [234]	No	No	No
Niaura 1994[a]	Yes [235]	No	No	No
Niaura 1999[a]	Yes [236]	No	No	No
NICLIB-9142-001	No	No	Yes [237]	Yes [154]
NICTDP3038	Yes [238]	Yes [239]/Yes [239]	Yes [240]	Yes [154]
NRA6430015[a]	Yes [241,242]	Yes [243]/No	No	No
Oncken 2007[a]	Yes [244,245]	No	No	No
Oncken 2008[a]	Yes [246]	Yes [247]/No	No	No
Oncken 2019[a]	Yes [248]	Yes [249]/Yes [249]	No	No
Ortega 2011[a]	Yes [250]	No	No	No
Pai 2012[a]	Yes [251]	No	No	No
Pirie 1992	Yes [252]	No	No	No
Pollak 2007[a]	Yes [253]	Yes [254]/No	No	No
Prapavessis 2007	Yes [255]	No	No	No
Puska 1979[a]	Yes [256]	No	No	No
Rennard 2006[a]	Yes [257]	No	No	No
S1420015	Yes [258]	No	Yes [259]	Yes [185]
Scherphof 2014[a]	Yes [260]	Yes [261,262]/No	No	No
Segnan 1991[a]	Yes [263,264]	No	No	No
Shiffman 2002	Yes [265-267]	No	No	No
SNAP[a]	Yes [268-270]	Yes [271,272]/Yes [271]	No	No
Stein 2013	Yes [31]	Yes [146]/Yes [146]	No	No
T89NT01	Yes [273-276]	No	Yes [277]	Yes [154]
T89NT07	Yes [278]	No	Yes [279]	Yes [154]
T90NI01	No	No	Yes [280]	Yes [154]
T90NI02	No	No	Yes [281]	Yes [154]
T90NI03	Yes [282]	No	Yes [283]	Yes [154]
T91NI04	Yes [284]	No	Yes [285]	Yes [154]

Table 2: Study pool of the benefit assessment (multipage table)

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry / result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Other documents**
T91NT08	No	No	Yes [286]	Yes [154]
T92NNIN002	Yes [287]	No	Yes [288]	Yes [154]
T92NNIN003	Yes [289]	No	Yes [290]	Yes [154]
T93NNPA004	Yes [291]	No	Yes [292]	Yes [154]
Tonnesen 2012	Yes [293]	No	No	No
Uyar 2007[a]	Yes [294]	No	No	No
Wisborg 2000[a]	Yes [295]	No	No	No
Wong 1999	Yes [296]	No	No	No
Yudkin 2003[a]	Yes [297,298]	No	No	No

a. The results of the study were not taken into account for the benefit assessment. Only studies from the study pool with reported outcome "permanent freedom from smoking" were taken into account, see Section 4.1.
b. Details on this study were not requested from the pharmaceutical company, as according to the pharmaceutical company, a dosage that was not in line with the SPC was used in the study. According to the publication, however, the dosage used corresponds to an application in line with the SPC. The study is therefore used for assessment on the basis of the publication.

SPC: Summary of Product Characteristics

Selection of studies for research questions 2, 3 and 4 based on suitable analyses of the outcome “permanent freedom from smoking”

The main relevant outcome of the present benefit assessment is permanent freedom from smoking, as the primary goal of the treatment of tobacco dependence is to achieve complete or permanent freedom from smoking (for the definition of the outcome "permanent freedom from smoking" used, see Chapter 3). Therefore, for research questions 3 and 4, only those studies from the study pool were considered in which the outcome "permanent freedom from smoking" was reported according to the definition described in Chapter 3 and was suitable for the benefit assessment. Prior to this, as described in more detail below, a possible bias in the results due to study selection based on reported results on the outcome “permanent freedom from smoking” (potential outcome reporting bias) was excluded with sufficient certainty. For research question 2 (cytisine), due to the limited evidence with only 3 RCTs, all studies in the study pool were considered for the benefit assessment, regardless of whether the outcome ”permanent freedom from smoking” in the studies on cytisine corresponded to the definition described in Chapter 3 (see Section 4.3).

For research question 3 (varenicline), the outcome “permanent freedom from smoking” was reported for 20 of the 38 studies and was suitable for the benefit assessment (see Table 2). In

the 20 studies analysed, 11 722 smokers were included in the relevant study arms. This corresponds to 74% of the relevant population of all 38 studies (N = 15 912). For 3 of the 18 studies not considered further (A3051045 [53], A3051072 [70] and A3051075 [75]), the clinical study report (CSR) is available and it can be ruled out that an evaluation of the outcome "permanent freedom from smoking" suitable for the benefit assessment was planned but not reported. For the other 15 studies that were not further analysed, there is also no indication from the publications or trial registry entries that an outcome suitable for the benefit assessment for permanent freedom from smoking was planned but not reported. In most of the studies not considered, the 7-day point prevalence outcome was reported instead. In the Cochrane Review Livingstone-Banks 2023 [23], 19 of the 20 studies considered in the benefit assessment and 17 of the 18 studies not considered further were examined independently of the available outcome operationalization for freedom from smoking. The strictest definition available in the studies was used for freedom from smoking. Thus, effect estimates for the definition of permanent freedom from smoking used in the present benefit assessment are presented together with effect estimates of 7-day point prevalence and other outcome definitions. There were no relevant differences in the effects observed for varenicline between the studies considered in the benefit assessment and the studies not considered further for the outcome "freedom from smoking" (in the strictest operationalizations available in each case) and the outcomes on AEs.

For research question 4 (nicotine), the outcome “permanent freedom from smoking” was suitable for the benefit assessment for 43 of the 100 studies (see Table 2). Only these 43 studies were considered in the further analyses for the benefit assessment. In total, 25 170 smokers were included in the relevant arms of the studies considered here. This corresponds to 46% of the relevant population of all 100 studies in the study pool (N = 55 266). A CSR is available for 2 of the studies not further considered in the analyses (96-NNCG-008 [156] and 97-NITG-001 [160]). Therefore, for these 2 studies, it can be ruled out that an analysis of the outcome suitable for benefit assessment was planned but not reported. In the Cochrane Reviews Hartmann-Boyce 2018 [21], Claire 2020 [25] and Fanshawe 2017 [24], 22 of the 43 (51%) studies considered in the benefit assessment and 40 of the 57 (70%) studies not further considered were examined. The 40 studies analysed in the Cochrane Reviews, which were not considered further here, used different definitions of freedom from smoking. The strictest definition available in the studies was used for the outcome “freedom from smoking”. In most of the studies, the 7-day point prevalence outcome was reported. There was no relevant difference in the effects between the studies considered in the benefit assessment and the studies not considered further for the relevant outcome "freedom from smoking" (in the strictest operationalizations available in each case). In the Cochrane Review Hartmann-Boyce 2018, a sensitivity analysis was also carried out with regard to the definition of freedom from smoking. The sensitivity analysis also showed no systematic difference in the effect estimate

between studies that reported permanent freedom from smoking and studies that only reported a 7-day point prevalence or where the outcome definition was unclear.

Irrespective of the aspects mentioned above, the most frequently used alternative outcome operationalization of 7-day point prevalence shows a clear correlation with the definition of permanent freedom from smoking used in the benefit assessment, whereby the effects in the 7-day point prevalence outcome tend to be greater [299]. Due to the clear correlation with other outcome definitions, it can be assumed that the reporting of the outcomes on freedom from smoking in the studies is largely independent of the results.

In summary, it can therefore be excluded with sufficient certainty that the non-inclusion of 18 studies on varenicline and 57 studies on nicotine due to a different outcome operationalization for the outcome "permanent freedom from smoking" has a relevant influence on the result of the present benefit assessment.

Studies on pregnant women and on adolescents

For research question 4 (nicotine), 8 relevant studies in pregnant smokers and 2 relevant studies in adolescents were identified. None of the studies reported the outcome "permanent freedom from smoking" in the operationalization suitable for the benefit assessment. These studies were therefore not considered further in the analyses for the benefit assessment due to the study selection described above on the basis of the outcome operationalization for the outcome "permanent freedom from smoking". All 8 identified studies on pregnant smokers were considered in the Cochrane Review Claire 2020. Both studies on adolescents were also examined in the Cochrane Review Fanshawe 2017. The effects for the available operationalization for freedom from smoking (mostly 7-day point prevalence) in the studies on pregnant women and adolescents do not contradict the results from the studies considered in the present benefit assessment. It is therefore assumed that the results of the benefit assessment are also transferable to the subpopulation of pregnant smokers as well as to adolescent smokers.

4.2 Bupropion and combinations in comparison with no drug treatment for smoking cessation (research questions 1 and 5)

For research question 1 (bupropion), 51 studies with potential relevance were identified (see Chapter A7). 14 of these studies were identified exclusively from the manufacturer's documents. Since the manufacturer did not provide any CSRs and no full publications of these studies were identified, the relevance of these studies could not be conclusively assessed. It is unclear how many smokers were included in these 14 studies and what proportion of the total population these 14 studies represent for research question 1. For research question 5 (combinations), 5 relevant studies and 1 potentially relevant study were identified (see Chapter A7). All studies investigate combinations with bupropion. For combinations with

bupropion, at least 1 additional potentially relevant study was identified from the manufacturer's documents, for which no CSR was provided. It is unclear what proportion of smokers this study represents and whether further studies would have been identified if the manufacturer had provided further documents. Due to the lack of data provided by the manufacturer, it was also not possible to test whether the severity of tobacco dependence was an effect modifier for bupropion, as the required subgroup analyses for the characteristic of severity of tobacco dependence were not provided.

Overall, there is a significant lack of data for research questions 1 and 5 on potentially relevant studies, a potential effect modification by the severity of tobacco dependence could not be investigated. An analysis based on the limited data available would potentially be highly biased and is therefore not carried out. Therefore, no benefit or harm can be derived for research questions 1 and 5.

4.3 Cytisine in comparison with no drug treatment for smoking cessation (research question 2)

Three relevant studies were identified for research question 2 (see Table 2). Only in 1 of the 3 studies the operationalization of the outcome "permanent freedom from smoking" was suitable for the benefit assessment [35], whereas in the other two studies an operationalization of the outcome "freedom from smoking" was used that was not suitable for the benefit assessment [33,37]. In the studies with unsuitable outcome operationalization (Dogar 2020 and West 2011), however, in addition to permanent freedom from smoking, the outcome of 7-day point prevalence was also reported, which in the present limited data situation is used as a sufficient approximation for permanent freedom from smoking for research question 2. However, subgroup analyses for the characteristic “severity of tobacco dependence” based on FTCD cut-off values for the outcome of permanent freedom from smoking or the outcome of 7-day point prevalence from author enquiries are only available for the Vinnikov 2008 study. Author enquiries about the Dogar 2020 and West 2011 studies were unsuccessful. As the Vinnikov 2008 study comprises only about 5% (N = 171) of the relevant population of all 3 studies, it remains unclear whether for the drug cytisine the characteristic “severity of tobacco dependence” represents an effect modifier for the outcome of permanent freedom from smoking or the outcome of 7-day point prevalence. Conclusions on the benefits of cytisine compared to no drug treatment in smokers with severe tobacco dependence are therefore not possible based on the results of the total population; subgroup analyses for the characteristic of severity of tobacco dependence are necessary for all 3 mentioned studies. Characteristics of the studies on cytisine and results on patient-relevant outcomes are additionally presented in sections A3.2.1 and A3.3.1, a conclusion on the benefit or harm cannot be derived based on the available data.

4.4 Varenicline in comparison with no drug treatment for smoking cessation (research question 3)

4.4.1 Characteristics of the studies included in the assessment

Out of the 38 studies in the study pool (see Table 2), the 20 studies that report the outcome of permanent freedom from smoking in the definition suitable for the benefit assessment were further considered (see Section 4.1).

The 20 studies include 12 manufacturer studies. These studies were provided with CSRs by the manufacturer Pfizer Pharma GmbH. Eight studies are investigator-initiated studies (IITs). There are no clinical CSRs available for these 8 studies.

All 20 studies were RCTs comparing varenicline in line with the SPC [20] with placebo. The treatment duration was usually 12 weeks. Only in the Stein 2013 study [31] the treatment duration was designed for 24 weeks. The study duration was 6 or 12 months. The studies were conducted in a period between 2001 and 2021. Most studies were conducted in Europe and/or North America. Two studies (A3051045 [53] and A3051055 [67]) were conducted exclusively in Asia. In 11 of the 20 studies, the 4-week abstinence rate (week 9 to 12) was the primary outcome. Permanent freedom from smoking as per the definition described in Chapter 3 was only the primary outcome in 3 studies.

The majority of the studies included smokers without severe disease or other special characteristics. Nevertheless, a large number of different accompanying diseases and characteristics are represented in the studies analysed. Two studies (ANRS144 Inter-ACTIV [94] and Ashare 2019 [96]) examined smokers who were infected with the human immunodeficiency virus (HIV). Only smokers with type 2 diabetes mellitus were included in the DIASMOKE study. The Stone 2013 study included smokers undergoing methadone treatment. The EVITA study [128] included smokers who had been hospitalized for acute coronary syndrome. Study A3051049 [61] investigated smokers with stable cardiovascular disease and study A3051054 [65] smokers with mild to moderate chronic obstructive pulmonary disease (COPD). Smokers with an accompanying psychiatric disorder were included in study A3051122 [88] (exclusively) and in the EAGLES/CATS study [27,28] (approximately 50% of the study population).

In most of the studies, the majority of smokers had already made at least 1 abstinence attempt before inclusion in the study. It is unclear whether these abstinence attempts were supported by medication. Only in studies A3051045, A3051055, A3051080 [78] and EAGLES/CATS more than 50% of participants had no prior abstinence attempt at baseline. All smokers in the study A3051139 [93] had already made at least one abstinence attempt under varenicline according to the inclusion criteria.

Section A3.2.2.1 presents the details of the individual studies.

Severity of tobacco dependence among smokers in the included studies and rationale for considering the total population

According to the mandate of the G-BA, only smokers with severe tobacco dependence according to the FTCD severity classification or analogously are included in the present research question. No relevant number of studies exist that exclusively investigated smokers with severe tobacco dependence. The included studies thus potentially contain mixed populations of smokers with low to severe tobacco dependence. In the following, the study populations are characterised in terms of the severity of tobacco dependence. Afterwards, reasons are given for taking the total population into account for the benefit assessment.

The mean value of the FTCD was between 4.4 and 6.0 in the included study populations. An FTCD value of < 4 (corresponding to minor to medium tobacco dependence) was found in less than 20% of the smokers in most studies, and a maximum of 28% (A3051045) (see Table 24 and Table 27 of the full report). Only in the Ashare 2019 study, no information on the FTCD or FTQ value of the study population was available. Here, daily smoking was an inclusion criterion and the average number of cigarettes smoked per day was 11. In the remaining studies, the average number of cigarettes per day at baseline ranged between 17 and 25, with the inclusion criteria being at least 10 cigarettes per day, in 2 studies (Cinciripini 2013 [108] and Cinciripini 2018 [110]) at least 5 cigarettes per day were required. The study populations analysed therefore mainly include smokers with moderate to severe tobacco dependence. The included studies therefore represent a broader population than the population covered by the G-BA's research question and cannot be used for the benefit assessment without further ado.

In order to investigate whether the included studies allow a conclusion on the benefit of varenicline in smokers with severe tobacco dependence on the basis of the overall population, subgroup analyses according to FTCD cut-off values for the relevant outcome “permanent freedom from smoking” were requested by the companies for the manufacturer studies (see Section A3.3.5.1). None of the requested FTCD cut-off values (4, 5 and 6) showed an effect modification for the outcome "permanent freedom from smoking" at month 6 or month 12. It is thus sufficiently ensured for the present benefit assessment that the severity of tobacco dependence has no relevant influence on the effect of varenicline on the relevant outcome "permanent freedom from smoking". Therefore, the total population of the studies is used to assess the benefit of varenicline in comparison with no drug treatment for smoking cessation in smokers with severe tobacco dependence and is considered for all relevant outcomes. For a critical reflection on this approach, see also Section A4.2.

4.4.2 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 20 studies. Table 3 presents an overview of the data available on patient-relevant outcomes from the included studies.

Table 3: Matrix of patient-relevant outcomes – varenicline (multipage table)

Study	Outcomes															
	Mortality	Morbidity			QoL	Side effects										
	All-cause mortality[a]	Permanent freedom from smoking at month 6	Permanent freedom from smoking at month 12	Other morbidity outcomes	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[b]	Cardiovascular side effects[a]	Neuropsychiatric side effects[a]	Dry mouth[a]	Fatigue[a]	Headache[a]	Nausea[a]	Itching[a]	Rash[a]	Irritations in the mouth and throat
A3051007/A3051018	●	●	●	–	○[c]	●	●	○[c]	●	●	●	●	●	●	●	( )
A3051028	●	●	●	–	○[c]	●	●	○[c]	●	●	●	●	●	●	●	( )
A3051036	●	●	●	–	○[c]	●	●	x	●	●	●	●	●	●	●	( )
A3051045	●	●	–	–	○[c]	●	●	x	●	●	●	●	●	●	●	( )
A3051049	●	●	●	–	–	●	●	○[c]	●	●	●	●	●	●	●	( )
A3051054	●	●	●	○[c]	–	●	●	○[c]	●	●	●	●	●	●	●	( )
A3051055	●	●	–	–	–	●	●	○[c]	●	●	●	●	●	●	●	( )
A3051080	●	●	–	–	–	●	●	○[c]	●	●	●	●	●	●	●	( )
A3051095	●	●	–	–	–	●	●	x	●	●	●	●	●	●	●	( )
A3051122	●	●	●	○[c]	–	●	●	x	●	●	●	●	●	●	●	( )
EAGLES/CATS	●	●	●	○[c]	–	●	●	○[c]	●	●	●	●	●	●	●	( )
A3051139	●	●	●	–	–	●	●	○[c]	●	●	●	●	●	●	●	( )
ANRS144 Inter-ACTIV	●	○[d]	●	–	x	●	●	–	●	○[c]	○[c]	○[c]	○[c]	○[c]	○[c]	( )
Ashare 2019	●	●	–	–	○[c]	●	–	–	○[c]	–	●	●	○[e]	–	–	( )
Cinciripini 2013	●	●	–	–	–	●	●	○[f]	○[c]	–	●	●	●	–	–	( )
Cinciripini 2018	●	●	●	–	–	●	●	–	●	●	●	●	●	–	○[g]	( )

Table 3: Matrix of patient-relevant outcomes – varenicline (multipage table)

Study	Outcomes															
	Mortality	Morbidity			QoL	Side effects										
	All-cause mortality[a]	Permanent freedom from smoking at month 6	Permanent freedom from smoking at month 12	Other morbidity outcomes	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[b]	Cardiovascular side effects[a]	Neuropsychiatric side effects[a]	Dry mouth[a]	Fatigue[a]	Headache[a]	Nausea[a]	Itching[a]	Rash[a]	Irritations in the mouth and throat
DIASMOKE	–	●	●	–	x	●	●	–	○[c]	–	●	●	●	–	–	( )
EVITA	●	●	●	–	–	●	–	○[c]	○[c]	–	–	●	●	–	–	( )
Niaura 2008	–	●	●	–	–	○[c]	●	–	○[c]	–	○[c]	○[c]	○[c]	–	–	( )
Stein 2013	●	●	–	–	–	●	●	○[c]	○[h]	○[h]	–	○[h]	○[h]	–	○[h]	( )

●: Data were reported and suitable.
○: Data were reported but unsuitable for the benefit assessment.
x: data were not reported despite the collection of these data being pre-specified
-: No data were reported (no further information) / The outcome was not surveyed.
( ): Outcome not relevant for varenicline due to the form of administration. Therefore, the outcome is not considered further for research question 3.
a. The longest reported period is considered in each case.
b. Treatment discontinuation due to AEs.
c. See the following text sections for reasons.
d. No values were reported. The values cannot be derived with sufficient accuracy from the figure shown in the publication.
e. There is no information on smokers with an event, but on the frequency of the event.
f. There is information for chest pain or cardiac AEs, but without indication of severity.
g. Separate data for rash acneiform and rash maculo-papular, each with 4 smokers with event. It is not meaningfully possible to summarise or limit the information to one of the details.
h. Only AEs assessed by the investigator as moderate or severe are reported. All manifestations, even mild ones, are considered relevant for the side effects under consideration. However, these were not taken into account in the available analyses.

AE: adverse event; QoL: health-related quality of life; SAE: serious adverse event

Other morbidity outcomes

Data on additional morbidity outcomes were reported in 3 studies. In study A3051054, in which smokers with mild to moderate COPD were included, the Clinical COPD Questionnaire (CCQ) was used. In the studies A3051122 and EAGLES/CATS, which included smokers with psychiatric disorders, several instruments were used to analyse psychiatric symptoms such as anxiety, depression or suicidality, including the Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS was also used in 2 further studies (A3051095 [83] and A3051139), which included smokers without an explicit psychiatric disorder. Overall, data on other morbidity outcomes are only available for a limited number of studies in the varenicline study pool. It is not assumed that the evaluation of these data would have a relevant influence on the conclusion of the benefit assessment. Other morbidity outcomes are therefore not considered further in the present benefit assessment of varenicline.

Health-related quality of life

Health-related quality of life was only recorded in 7 studies. The registry entry for the ANRS144 Inter-ACTIV study indicates that data collection was planned via the Short Form-12 Health Survey (SF-12). However, the results were not reported. In the DIASMOKE study, the Diabetes Quality of Life (QoL) Questionnaire was used according to the study protocol. However, no results were reported. In the studies A3051007/A3051018 [40,41], A3051028 [46], A3051036 [50], and A3051045 the Smoking Cessation Quality of Life (SCQoL) questionnaire was used. Only descriptive analyses are available. The Ashare 2019 study used the HIV/Acquired Immune Deficiency Syndrome (AIDS)-Targeted Quality of Life scale. Only results for week 12 are shown in the registry entry. Overall, only a few instruments were used to record health-related quality of life, the results of which were either not reported or only inadequately reported. Therefore, the outcome “health-related quality of life” is not considered further in the present benefit assessment.

Side effects

In all studies, usable data were recorded and reported for at least one outcome in the side effects category. In the ANRS144 Inter-ACTIV study, however, only specific AEs were reported for which a causal relationship with the treatment was suspected. Therefore, in this study, only the data on SAEs, discontinuation due to AEs, and neuropsychiatric side effects are suitable for benefit assessment. In the Niaura 2008 study [143], only events for which a causal relationship with nicotine abstinence was suspected were recorded. Therefore, in this study only the data on discontinuation due to AEs are suitable for benefit assessment.

Cardiovascular side effects

To ensure the patient relevance of the outcome “cardiovascular side effects”, this was defined as major adverse cardiovascular events (MACE) or cardiovascular SAEs e.g. operationalized as SAEs in the SOC “cardiac disorders”).

MACE are only reported for the EAGLES/CATS and EVITA studies [129]. In the EAGLES/CATS study, MACE were defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. In the definition of MACE+, the occurrence or worsening of peripheral vascular disorders requiring intervention, coronary revascularizations, and hospitalizations due to unstable angina were also taken into account. Other serious cardiovascular side effects are not covered by the definition. In the EVITA study, the MACE outome is composed of cardiovascular deaths, myocardial infarction, and unstable angina. Other serious cardiovascular side effects are not covered by the definition.

The overall rates of SAEs are reported in most studies. However, almost all studies lack analyses of the number of smokers with SAEs in the cardiac disorders SOC or a comparable operationalization suitable for benefit assessment. Only for the Stein 2013 study, the registry entry states that merely 1 smoker in the nicotine arm had 1 cardiovascular SAE. Lists of frequent AEs sorted by SOC and PT are available in the studies for which CSRs are available. However, these lists do not specify whether these are SAEs, so that no results for the outcome of SAE in the SOC “cardiac disorders” can be derived from them for the benefit assessment. Lists of SAEs, in which details of each SAE are presented, are available in the studies marked with o in the matrix (see Table 3). However, the data from these lists are not suitable for the benefit assessment, as they usually mention PTs, sometimes several, and no SOCs clearly underlying the SAE. These lists are missing or blacked out in the studies marked with x in Table 3.

In total, only 3 studies provide potentially suitable analyses of MACE or cardiovascular SAEs. Therefore, the benefit assessment will refrain from further consideration of differently defined outcomes for MACE from the EAGLES/CATS and EVITA studies as well as the report on 0 cardiovascular SAEs in the varenicline arm and the placebo arm of the Stein 2013 study.

Irritations in the mouth and throat

This outcome was named in the report plan independently of the drug to be investigated as a patient-relevant outcome. However, as varenicline, in contrast to nicotine, is not administered orally via the mouth and throat, but is only taken as a tablet, irritation of the mouth and throat is not a relevant AE for varenicline and is not considered in the benefit assessment for research question 3.

4.4.3 Assessment of the risk of bias of the results

A total of 20 studies were included in the analyses of the present benefit assessment of varenicline. Of these, 4 studies were assessed across outcomes as having a high risk of bias due to unclear information on randomization and/or allocation concealment. The remaining 16 studies were evaluated across outcomes with a low risk of bias in the results.

In terms of outcome-specific risk of bias, only 8 and 3 of the total of 20 studies were rated as having a low risk of bias for the results of permanent freedom from smoking at month 6 and month 12, respectively. The most common reason for a high risk of bias was a high or unclear number of patients who discontinued the study at month 6 or month 12 (7 and 9 studies, respectively). The risk of bias in the results of the other studies was already assessed as high across outcomes or the studies did not report any (suitable) data.

In 7 studies, the results of the outcome "all-cause mortality" were assessed as having a low risk of bias. In the results of 7 studies, the risk of bias was high due to high study discontinuation rates, in the results of 4 studies a high risk of bias was already identified across outcomes. Two studies reported no (usable) data.

For the overall rate of SAEs, the results of 12 studies show a low risk of bias. In the results of 4 studies, the risk of bias was already rated as high across outcomes, additional results from 3 studies were rated with a high risk of bias due to high study discontinuation rates. For 1 study, data were reported that were not suitable for the benefit assessment. For the remaining AE outcomes, there are 5 or 6 studies each with a low risk of bias in the results. The reasons for a high risk of bias are primarily the lack of blinding in the collection of subjective outcome results as well as the high study discontinuation rates.

Detailed information on the risk of bias across outcomes and on the outcome-specific risk of bias can be found in Table 49 of the full report.

4.4.4 Results on patient-relevant outcomes

Potential evidence base given the available data

The evidence base was initially derived separately for each outcome according to the methodology described in the report plan (see sections A2.3.3 and A2.3.6) and in the General Methods 6.1 of the Institute [300]. As shown in Section 4.4.3 and in Table 49 of the full report, there are outcome-specific studies with high and low risk of bias in the results. The outcome-specific assessment of the risk of bias reveals a moderate or high certainty of results. Initially, only the studies with high qualitative certainty of results are considered. The conclusions about the evidence base derived from the studies with high qualitative certainty of results cannot be weakened by including the studies with moderate qualitative certainty of results, but rather enhanced. Furthermore, when deriving conclusions for the evidence base, the principles described in detail in the General Methods 6.1 of the Institute [300] apply.

As described in Section 4.4.1, the total population of the studies is used to assess the benefit of varenicline in comparison with no drug treatment for smoking cessation in smokers with severe tobacco dependence, and is considered for all patient-relevant outcomes. As subgroup analyses for the characteristic of severity of tobacco dependence based on FTCD cut-off values

are only available for the outcome relevant for benefit assessment, i.e. permanent freedom from smoking, conclusions about the benefit or harm of varenicline based on the total population for the other outcomes are associated with a higher degree of uncertainty. Due to this uncertainty, it cannot be clarified to the same extent for these outcomes whether there are potentially other or further advantages or disadvantages of varenicline for smokers with severe tobacco dependence in comparison with no drug treatment for smoking cessation. Therefore, the certainty of conclusions is downgraded for all outcomes with the exception of permanent freedom from smoking. Overall, on the basis of the available information for the outcome "permanent freedom from smoking", maximum proof, for example for a greater benefit, can be derived. For all other outcomes, on the other hand, no more than indications can be derived.

Subgroup characteristics and other effect modifiers

Subgroup analyses were conducted based on FTCD or FTQ cut-off values for the present benefit assessment to examine potential effect modification by the severity of tobacco dependence. As no relevant effect modification was shown here, the overall population is used for the benefit assessment (see Section 4.4.1).

According to the report plan, subgroup analyses by age (12 to 17 years/18 to 65 years/> 65 years), by sex, and by mental comorbidities were also planned. However, subgroup analyses according to these factors are generally not available in the studies on varenicline for the outcomes considered in the benefit assessment. Only study A3051139 provides suitable analyses separately for men and women for the outcome of permanent freedom from smoking at month 12. Adolescents (age group 12 to 17 years) are not covered by the approval of varenicline; none of the studies included smokers under 18 years of age. The mean age of smokers in the 20 studies considered ranges between 40 and 57 years. In the studies for which corresponding data are available, at least 82% of the study participants are in the age group 18 to 65 years (see Section A3.2.2.1). Based on the available data, however, it is not possible to assess whether there was an effect modification by the characteristic of age.

In the studies, the proportions of female and male smokers were largely balanced, with a tendency towards more male smokers than female ones. Only the studies A3051045, A3051049 and A3051055 included significantly more men than women (approx. 78% to 97% men). There were no systematic differences in the effects for the outcomes analysed between the studies with a high proportion of men and the other studies. In the subgroup analysis of study A3051139, there was an effect modification by the characteristic of sex. Based on the available data, however, it is not possible to conclusively examine whether there was an effect modification by the characteristic of sex.

Smokers with mental comorbidities were included in 1 of 2 cohorts of the EAGLES/CATS study. Smokers with major depression were included in study A3051122 in accordance with the inclusion criteria. There was no systematic difference in the effects between the EAGLES/CATS and A3051122 studies and the other studies for any of the outcomes analysed.

While effect modifications for the subgroup characteristics defined in the report plan cannot be conclusively assessed in the present data situation, there are no signs overall that there is a relevant effect difference between the subgroups specified in the report plan. The benefit conclusion is therefore derived based on the total population without taking into account subgroup characteristics.

4.4.4.1 Results on all-cause mortality

For the outcome “all-cause mortality”, results were reported in 18 studies. In each case, the longest reported survey period was used for the benefit assessment. All-cause mortality was reported in 16 studies until the end of the study. In 2 studies, data are only available up to the end of treatment or up to 30 days after the end of treatment. Overall, the all-cause mortality was low. No statistically significant difference between the treatment groups was shown for the outcome of all-cause mortality (see Section A3.3.2.2). There is no hint of greater or lesser harm from varenicline in comparison with no drug treatment for smoking cessation.

4.4.4.2 Results on permanent freedom from smoking at month 6 and at month 12

As described in Section 4.1, only studies that have reported the outcome of permanent freedom from smoking at month 6 and/or month 12 were considered in the analyses. Suitable data on permanent freedom from smoking at month 6 are available for 19 studies. 13 of the 20 studies have a longer observation period, so that data on permanent freedom from smoking are available at month 12.

Due to significant heterogeneity, a meta-analytical summary of the results at month 6 was not meaningfully possible, both when looking at the studies with high certainty of results and when looking at the studies with high and moderate certainty of results. Therefore, a qualitative summary of the results on permanent freedom from smoking was made at month 6. There are clearly conclusive effects in favour of varenicline when looking at the studies with high certainty of results. This results in a proof of a greater benefit from varenicline versus placebo for permanent freedom from smoking at month 6 (see Section A3.3.2.3).

For permanent freedom from smoking at month 12, when considering the studies with high certainty of results, it becomes apparent that the combined effect is not informative and that moderately conclusive effects are present. The analysis of the studies with high and moderate certainty of results clearly shows conclusive effects between the treatment groups in favour

of varenicline (see Section A3.3.2.4). This results in a proof of a greater benefit from varenicline versus no drug treatment for smoking cessation for permanent freedom from smoking at month 12 (see Section A3.3.2.3).

4.4.4.3 Results on serious adverse events

Suitable data for the outcome of SAEs are available from 19 studies. In each case, the longest reported survey period was used for the benefit assessment. In 7 studies, data are available up to the end of the study. In 12 studies, data are available up to shortly (7 or 30 days) after the end of treatment. No statistically significant difference between the treatment groups was shown for the outcome of SAEs (see Section A3.3.2.5). There is no hint of greater or lesser harm from nicotine in comparison with no drug treatment for smoking cessation.

4.4.4.4 Results on discontinuation due to adverse events

Discontinuations due to AEs were reported in 18 of the 20 studies. In all of these studies, treatment was discontinued due to AEs. The outcome survey period corresponds to the treatment duration, which was usually 12 weeks. Only the Stein 2013 study allowed treatment for up to 24 weeks, meaning that treatment discontinuations due to AEs were also reported for this period. When analysing the results of the studies with high certainty of results, there was no statistically significant difference between the treatment groups. The analysis of the studies with high and moderate certainty of results shows a statistically significant difference between the treatment groups to the disadvantage of varenicline (see Section A3.3.2.6). There is a hint of greater harm from varenicline in comparison with no drug treatment for smoking cessation.

4.4.4.5 Results on neuropsychiatric side effects

In the 12 studies for which CSRs including detailed tables on AEs were available, suitable data were available for the benefit assessment. Of the 8 studies for which no CSRs are available only the ANRS144 Inter-ACTIV and Cinciripini 2018 studies reported neuropsychiatric side effects in a form suitable for benefit assessment. Thus, suitable data for the benefit assessment were reported in 70% of the studies in the study pool analysed. In each case, the longest reported survey period was used for the benefit assessment. In most cases, neuropsychiatric side effects were only reported until shortly (7 or 30 days) after the end of treatment.

For the benefit assessment, all reported events in the SOC “psychiatric disorders” were used. This includes the PTs “abnormal dreams”, “sleep disorders” and “depression”. The detailed tables on SOCs and PTs in the CSRs show that the most common PTs in the SOC were “psychiatric disorders” “insomnia” and “abnormal dreams”. In the ANRS144 Inter-ACTIV study, no information is available on the details of the evaluation of psychiatric side effects. In the Cinciripini 2018 study, sleep disorders, irritability and abnormal dreams were the most

common events. It remains unclear whether the frequently occurring PTs “sleep disorders”, “irritability” and “abnormal dreams” are side effects or withdrawal symptoms.

The analysis of the studies with high certainty of results shows a statistically significant difference between the treatment groups to the disadvantage of varenicline (see Section A3.3.2.7). There is an indication of greater harm from varenicline in comparison with no drug treatment for smoking cessation.

4.4.4.6 Results on specific adverse events

In the 12 studies for which CSRs including detailed tables on AEs were available, suitable data were available for the benefit assessment of varenicline versus placebo with regard to all considered specific AEs. Of the 8 studies for which no CSRs are available, itching and rash were not reported in an appropriate manner in any of these studies. For dry mouth, fatigue, headache and nausea, results suitable for the benefit assessment were reported in up to 5 studies without a CSR (see Table 3). In each case, the longest reported survey period was used for the benefit assessment. In most cases, specific AEs were only reported until shortly (7 or 30 days) after the end of treatment.

Results on dry mouth

For 13 of the 20 studies considered (65%), analyses are available for the outcome of dry mouth in a form suitable for benefit assessment. Apart from the Cinciripini 2018 study, the results of the outcomes were only reported until shortly (7 or 30 days) after the end of treatment. For the outcome “dry mouth”, when considering the studies with high certainty of results, there was no statistically significant difference between the treatment groups. The analysis of the studies with high and moderate certainty of results shows a statistically significant difference between the treatment groups to the disadvantage of varenicline (see Section A3.3.2.8). There is a hint of greater harm from varenicline in comparison with no drug treatment for smoking cessation.

Results on fatigue

For 16 of the 20 studies considered (80%), data for the outcome of fatigue are available in a form suitable for benefit assessment. Apart from the Cinciripini 2013 and Cinciripini 2018 studies, the results of the outcomes were only reported until shortly (7 or 30 days) after the end of treatment. For the outcome “fatigue”, a statistically significant difference between the treatment groups to the disadvantage of varenicline was observed in the studies with high certainty of results (see Section A3.3.2.9). There is an indication of greater harm from varenicline in comparison with no drug treatment for smoking cessation.

Results on headaches

For 17 of the 20 studies considered (85%), data for the outcome of headaches are available in a form suitable for benefit assessment. Apart from the Cinciripini 2013 and Cinciripini 2018 studies, the results of the outcomes were only reported until shortly (7 or 30 days) after the end of treatment. For the outcome “headaches”, when considering the studies with high certainty of results, there was no statistically significant difference between the treatment groups. The analysis of the studies with high and moderate certainty of results shows a statistically significant difference between the treatment groups to the disadvantage of varenicline (see Section A3.3.2.10). There is a hint of greater harm from varenicline in comparison with no drug treatment for smoking cessation.

Results on nausea

For 16 of the 20 studies considered (80%), data for the outcome of nausea are available in a form suitable for benefit assessment. Apart from the Cinciripini 2013 and Cinciripini 2018 studies, the results of the outcomes were only reported up to or until shortly after the end of treatment. For the outcome “nausea”, a statistically significant difference between the treatment groups to the disadvantage of varenicline was observed in the studies with high certainty of results (see Section A3.3.2.11). There is an indication of greater harm from varenicline in comparison with no drug treatment for smoking cessation.

Results on itching and rash

For 12 of the 20 studies considered (60%), data for the outcome of itching and for the outcome of rash are available in a form suitable for benefit assessment. No statistically significant difference between the treatment groups was shown for both outcomes (see sections A3.3.2.12 and A3.3.2.13). In each case, there is no hint of greater or lesser harm from varenicline in comparison with no drug treatment for smoking cessation.

4.4.5 Overall evaluation of results – varenicline

Evidence map

The following Table 4 shows the evidence map regarding patient-relevant outcomes.

Table 4: Evidence map for varenicline vs. no drug treatment regarding patient-relevant outcomes

Comparison / Outcome category / Outcome	Varenicline vs. no drug treatment
Mortality	
All-cause mortality	⇔
Morbidity	
Permanent freedom from smoking (at month 6)	⇑⇑
Permanent freedom from smoking (at month 12)	⇑⇑
Other morbidity outcomes	–
Health-related quality of life	–
Side effects	
SAEs	⇔
Discontinuation due to AEs	↘
Cardiovascular side effects	–
Neuropsychiatric side effects	⇓
Dry mouth	↘
Fatigue	⇓
Headache	↘
Nausea	⇓
Itching	⇔
Rash	⇔
Irritations in the mouth and throat	–[a]

⇑⇑: Proof of (greater) benefit or proof of lesser harm from varenicline vs. no drug treatment.
⇓: Indication of lesser benefit or indication of (greater) harm from varenicline vs. no drug treatment.
↘: Hint of lesser benefit or hint of (greater) harm from varenicline vs. no drug treatment.
⇔: No hint, indication, or proof; homogeneous result
-: No usable data reported
a. The outcome is not relevant for varenicline and is therefore not considered further for research question 3.
AE: adverse event; SAE: serious adverse event

Assessment of the volume of unpublished data

For all studies for which CSRs were available, full publications were also available. Therefore, there are no indications of relevant unpublished data for research question 3. No relevant studies without reported results were identified for the drug varenicline. As described in Section 4.4.2, results on health-related quality of life were inadequately reported. For the present benefit assessment, however, there is no overall limitation of certainty of conclusions due to unpublished data.

Weighing of benefits versus harms

From the observation of the outcome of permanent freedom from smoking at month 6 and month 12 in the total study population, there is proof of a greater benefit of varenicline in comparison with no drug treatment for smoking cessation. The observation of outcomes related to side effects provides indications or hints of greater harm from varenicline in comparison with no drug treatment for smoking cessation in the outcomes of discontinuation due to AEs, neuropsychiatric side effects, dry mouth, fatigue, headaches, and nausea. The outcomes related to side effects were generally reported for a shorter period – usually over the course of the treatment duration or slightly beyond – than the results of the outcome of permanent freedom from smoking, and therefore do not cover the entire course of the study. In the present therapeutic indication, AEs and withdrawal symptoms cannot be clearly distinguished from each other, so potentially withdrawal symptoms have also been included in the analysis of the AEs considered here. This is particularly suspected in the case of neuropsychiatric side effects such as sleep disorders, abnormal dreams, and irritability. No statistically significant differences are evident in the outcomes of all-cause mortality and SAEs. The greater harm of varenicline in some outcomes related to side effects does not call into question the overall benefit in the outcome relevant for the benefit assessment, which is permanent freedom from smoking.

Suitable data for the assessment were not available for all outcomes. However, it is not assumed that these missing data have a relevant influence on the conclusion.

In summary, there is proof of a greater benefit of varenicline in comparison with no drug treatment for smoking cessation in smokers with severe tobacco dependence.

4.5 Nicotine in comparison with no drug treatment for smoking cessation (research question 4)

4.5.1 Characteristics of the studies included in the assessment

For the drug nicotine, 100 relevant studies were identified (see Section A3.1.3). In 43 studies, the outcome of permanent freedom from smoking was reported in the operationalization suitable for benefit assessment. Only these studies are considered in the following analyses (see Section 4.1). Out of 43 studies, 24 are manufacturer studies for which CSRs are available. The remaining 19 studies are studies for which no CSRs, but full publications were available. Hereinafter, these studies are referred to as "IITs". However, it cannot be ruled out that pharmaceutical companies were also study sponsors in some of these studies.

All 43 studies were RCTs in which different administration forms of nicotine or a combination of a transdermal patch and another administration form were investigated. The majority of the studies were placebo-controlled. In 3 IITs, a combination of nicotine and a non-drug treatment was compared to a sole non-drug treatment in an open-label (Pirie 1992 [252],

Prapavessis 2007 [255]) or single-blind (Harackiewicz 1988 [208]) study design. The application of the various nicotine preparations was largely in line with the respective SPCs. Depending on the administration form under investigation, the treatment duration ranged from a minimum of 6 weeks to a maximum of 18 months, depending on the study. The study durations were between 6 months and 24 months. The manufacturer studies were conducted in a period between 1989 and 2016. Information on the period of study implementation is not available for all IITs. The IITs for which data are available were carried out between 1981 and 2017. The studies were mainly conducted in Europe and/or the United States. One study each was conducted exclusively in Asia (CHN-Nicotine Mint Lozenge-002 [183]) and Africa (Abdelghany 2022 [174]). The primary goal of treatment in the vast majority of studies was to achieve freedom from smoking. In 7 studies, however, the primary study objective was merely a reduction in smoking.

The studies generally included adult smokers without serious pre-existing conditions. Only the Joseph 1996 study [226] examined smokers from the age of 45 with ≥ 1 cardiovascular disorder or cerebrovascular condition. The EAGLES/CATS study [27,28] included smokers with a stable psychiatric disorder in 1 of the 2 cohorts. The Hughes 2003 study [220] included smokers with a history of alcohol dependence, and the Stein 2013 study [31] included smokers undergoing methadone treatment. In most of the studies for which corresponding data were available, the majority of the smokers included had already made at least one abstinence attempt. It is unclear whether these abstinence attempts were supported by medication.

Further information on the individual studies and the characterisation of the study populations can be found in Section A3.2.3.

Severity of tobacco dependence among smokers in the included studies and rationale for considering the total population

According to the mandate of the G-BA, only smokers with severe tobacco dependence according to the FTCD severity classification or analogously are included in the present research question. No relevant number of studies exist that exclusively investigated smokers with severe tobacco dependence. The included studies thus potentially contain mixed populations of smokers with low to severe tobacco dependence. In the following, the study populations are characterised in terms of the severity of tobacco dependence. Afterwards, reasons are given for taking the total population into account for the benefit assessment.

Information on the severity of tobacco dependence is based on the FTCD or the FTQ, depending on the study. The mean value of the FTCD or FTQ in the included study populations ranged between 3.7 and 7.8. An FTCD or FTQ value < 4 (corresponding to minor to moderate tobacco dependence) was found in the manufacturer studies for 0% to a maximum of 26% (NICLIB-9142-001) of the smokers (see Table 32 of the full report). Information on the

proportion of smokers with an FTCD or FTQ value < 4 is missing in the IITs, with the exception of the Abdelghany 2022 study (see Table 35 of the full report). In the Abdelghany 2022 study, none of the included smokers showed an FTCD value < 4. In 5 IITs, no information was reported on the severity of tobacco dependence according to FTCD or FTQ. For the studies Hjalmarson 1984 [210], Pirie 1992 and Harackiewicz 1988, data are available on the average number of cigarettes smoked per day. Smokers included in the Hjalmarson 1984 study reported smoking an average of about 24 cigarettes per day at baseline. In the Pirie 1992 study, this value was around 26 cigarettes and in the Harackiewicz 1988 study it was 27 cigarettes. For the remaining two studies (Prapavessis 2007, Wong 1999 [296]), information on the average number of cigarettes smoked per day is missing, however, in both studies, daily smoking of at least 10 cigarettes was an inclusion criterion. The study populations analysed therefore mainly include smokers with moderate to severe tobacco dependence. The included studies therefore represent a broader population than the population covered by the G-BA's research question and cannot be used for the benefit assessment without further ado.

In order to investigate whether the included studies nevertheless allow a conclusion on the benefit of nicotine in smokers with severe tobacco dependence on the basis of the overall population, subgroup analyses according to FTCD or FTQ cut-off values for the relevant outcome “permanent freedom from smoking” were requested for the manufacturer studies by the pharmaceutical companies (see Section A3.3.5.2). None of the requested FTCD or FTQ cut-off values (4, 5 and 6) showed an effect modification for the outcome "permanent freedom from smoking" at month 6 or month 12. It is thus sufficiently ensured for the present benefit assessment that the severity of tobacco dependence has no relevant influence on the effect of nicotine on the relevant outcome "permanent freedom from smoking". Therefore, the total population of the studies is used to assess the benefit of nicotine in comparison with no drug treatment for smoking cessation in smokers with severe tobacco dependence and is considered for all outcomes. For a critical reflection on this approach, see also Section A4.2.

4.5.2 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 43 studies. Table 5 presents an overview of the data available on patient-relevant outcomes from the included studies.

Table 5: Matrix of relevant outcomes – nicotine (multipage table)

Study	Outcomes																
	Mortality	Morbidity			QoL	Side effects											
	All-cause mortality[a]	Permanent freedom from smoking at month 6	Permanent freedom from smoking at month 12	Other morbidity outcomes	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[b]	Cardiovascular side effects[a]	Neuropsychiatric side effects[a]	Dry mouth[a]	Fatigue[a]	Headache[a]	Nausea[a]	Itching[a]	Rash[a]	Irritations in the mouth and throat[a]
94NNBT011	–	●	●	–	–	●	●[c]	○[d]	( )	●	●	●	●	●	●	○[e]
94NNBT012	–	●	●	–	–	●	●[c]	●	( )	●	●	●	●	●	●	●
96-NNIN-016	●	●	●	○[d]	○[d]	●	●[c]	○[d]	( )	●	●	●	●	●	●	●
980-CHC-1013-028	●	●	●	○[d]	–	●	●	○[d]	( )	●	●	●	●	●	●	●
980-CHC-9021-013	○[f]	●	●	○[d]	○[d]	●	●[c]	○[d]	( )	●	●	●	●	●	●[g]	●
98-NNCG-014	○[h]	●	●	○[d]	○[d]	○[i]	●[c]	○[d]	( )	●	●	●	●	●	●	●
98-NNCG-017	●	●	●	○[d]	○[d]	●	●[c]	○[d]	( )	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]
98-NNIN-027	●	●	●	○[d]	○[d]	●	●[c]	○[d]	( )	●	●	●	●	●	●	●
EAGLES/CATS	●	●	●	○[d]	–	●	●	●	( )	●	●	●	●	●	●	●
A6431111	●	●	●	–	–	●	●	●	( )	●	●	●	●	●	●	●
NICLIB-9142-001	●	●	–	–	–	●	●[c]	○[d]	( )	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]
NICTDP3038	●	●	–	–	–	●	●[c]	○[d]	( )	●	●	●	●	●	●	●
T89NT01	–	●	●	–	–	x	●[c]	–	( )	●	●	●	●	●	●[j]	●
T89NT07	–	●	●	–	–	x	●[c]	–	( )	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]
T90NI01	–	●	●	○[d]	–	●	●[c]	○[d]	( )	●	●	●	●	●	●	●

Table 5: Matrix of relevant outcomes – nicotine (multipage table)

Study	Outcomes															
	Mortality	Morbidity			QoL	Side effects										
	All-cause mortality[a]	Permanent freedom from smoking at month 6	Permanent freedom from smoking at month 12	Other morbidity outcomes	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[b]	Cardiovascular side effects[a]	Neuropsychiatric side effects[a]	Dry mouth[a]	Fatigue[a]	Headache[a]	Nausea[a]	Itching[a]	Rash[a]	Irritations in the mouth and throat[a]
T90NI02	●	●	●	–	–	●	●[c]	○[d]	( )	●	●	●	●	●	●	●
T90NI03	–	●	●	–	–	●	●[c]	○[d]	( )	●	●	●	●	●	●	●
T91NI04	–	●	●	–	–	●	●	●	( )	●	●	●	●	●	●	●
T91NT08	–	●	●	–	–	●	●	○[d]	( )	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]
T92NNIN002	–	●	●	–	–	●	●[c]	○[d]	( )	●	●	●	●	●	●	●
T92NNIN003	–	●	●	–	–	●	●[c]	○[d]	( )	●	●	●	●	●	●	●
T93NNPA004	●	●	●	x	–	●	●	○[d]	( )	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]	○[d]
CHN-Nicotine Mint Lozenge-002	●	●	–	–	–	●	●	○[d]	( )	●	●	●	●	●	●	●
S1420015	●	●	–	–	–	●	●[c]	●	( )	●	●	●	●	●	●	●
Abdelghany 2022	●	●	–	–	–	●	–	●	( )	–	–	○[k]	–	–	–	–
Bolliger 2000	–	–	●	–	x	○[l]	●[c]	–	( )	–	–	–	●[m]	–	–	●
Daughton 1998	–	●	●	–	–	–	–	–	( )	–	–	–	–	–	–	–
Garvey 2000	–	–	●	○[d]	–	–	●[c]	–	( )	–	–	–	○[n]	–	–	–
Gourlay 1995	–	●	–	–	–	–	○[o]	–	( )	–	–	○[o]	○[o]	–	–	–
Harackiewicz 1988	–	●	●	–	–	–	–	–	( )	–	–	○[p]	○[p]	–	–	–

Table 5: Matrix of relevant outcomes – nicotine (multipage table)

Study	Outcomes															
	Mortality	Morbidity			QoL	Side effects										
	All-cause mortality[a]	Permanent freedom from smoking at month 6	Permanent freedom from smoking at month 12	Other morbidity outcomes	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[b]	Cardiovascular side effects[a]	Neuropsychiatric side effects[a]	Dry mouth[a]	Fatigue[a]	Headache[a]	Nausea[a]	Itching[a]	Rash[a]	Irritations in the mouth and throat[a]
Hjalmarson 1984	●	●	●	–	–	●	–	●	( )	–	–	–	–	–	–	●
Hughes 1989	–	–	●	–	–	–	●[c]	–	( )	–	–	–	●	–	–	–
Hughes 1990	–	●	–	–	–	–	–	–	( )	–	–	–	○[q]	–	–	–
Hughes 2003	●	●	–	○[d]	–	●	●[c]	●	( )	–	–	–	–	–	–	–
Jensen 1990	–	●	●	–	–	–	–	–	( )	–	–	–	–	–	–	○[r]
Jorenby 1999	–	○[s]	●	○[d]	–	●	●	●	( )	●	–	●	●	–	–	–
Joseph 1996	●	●	–	–	–	○[t]	–	○[d]	( )	○[u]	–	–	–	–	–	–
Pirie 1992	–	●	●	–	–	–	–	–	( )	–	–	–	–	–	–	–
Prapavessis 2007	–	–	●	○[d]	–	–	–	–	( )	–	–	–	–	–	–	–
Shiffman 2002	●	●	●	–	–	●	●	–	( )	–	–	●	●	–	–	–
Stein 2013	●	●	–	–	–	●	●	●	( )	○[v]	–	○[v]	○[v]	–	○[v]	–
Tonnesen 2012	●	●	●	–	–	●	●	–	( )	○[d]	–	○[d]	○[d]	–	–	○[d]
Wong 1999	–	●	–	–	–	●	●	●	( )	–	–	○[w]	–	–	–	–

Table 5: Matrix of relevant outcomes – nicotine (multipage table)

Study	Outcomes																
	Mortality	Morbidity			QoL	Side effects											
	All-cause mortality[a]	Permanent freedom from smoking at month 6	Permanent freedom from smoking at month 12	Other morbidity outcomes	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[b]	Cardiovascular side effects[a]	Neuropsychiatric side effects[a]	Dry mouth[a]	Fatigue[a]	Headache[a]	Nausea[a]	Itching[a]	Rash[a]	Irritations in the mouth and throat[a]

●: Data were reported and suitable.
○: Data were reported but unsuitable for the benefit assessment.
x: data were not reported despite the collection of these data being pre-specified
-: No data were reported (no further information)/The outcome was not surveyed.
( ): Outcome not relevant for nicotine. Therefore, the outcome is not considered further for research question 4.
a. The longest reported period is considered in each case.
b. Treatment discontinuation due to AEs; deviations are marked accordingly.
c. It is unclear whether the information refers to treatment discontinuation or study discontinuation.
d. See the following text sections for reasons.
e. Data on irritation in the mouth and throat are available separately for treatment weeks 1+2, 3+4 and 5+6. It is not meaningfully possible to summarise the data.
f. There were 2 deaths in the study, but it was not reported in which arms these occurred.
g. Data are only available for PT "erythematous rash".
h. There was 1 death in the study, but it was not reported in which arm this occurred.
i. In the study, SAEs occurred in 8 smokers, but it was not reported in which arms these occurred.
j. Data are only available for PT "rash papular".
k. The p-value for the comparison of nicotine vs. placebo was reported. There were no events in the nicotine arm, but no data on smokers with events in the placebo arm are available.
l. There were a total of 53 SAEs in the study, but it was not reported in which arms these occurred.
m. Data are only available for "nausea or nausea/vomiting".
n. Only a summarized analysis of common AEs (including nausea) was reported.

Table 5: Matrix of relevant outcomes – nicotine (multipage table)

Study	Outcomes																
	Mortality	Morbidity			QoL	Side effects											
	All-cause mortality[a]	Permanent freedom from smoking at month 6	Permanent freedom from smoking at month 12	Other morbidity outcomes	Health-related quality of life	SAEs[a]	Discontinuation due to AEs[b]	Cardiovascular side effects[a]	Neuropsychiatric side effects[a]	Dry mouth[a]	Fatigue[a]	Headache[a]	Nausea[a]	Itching[a]	Rash[a]	Irritations in the mouth and throat[a]

o. Data on AEs are only available for 179 of 315 smokers in the nicotine arm and 143 of 314 smokers in the placebo arm.
p. Only data for the self-help arm and the control arm combined were reported. The relevant comparator arm for the benefit assessment is the self-help arm. Therefore, no suitable data are available.
q. Data were reported for the first week after smoking cessation only.
r. The p-value for the comparison of nicotine gum vs. regular gum was reported. However, no data on the number of smokers with an event are available.
s. No values were reported. The values cannot be derived with sufficient accuracy from the figure shown in the publication.
t. A selection of SAEs that was defined a priori was reported. Therefore, it cannot be assumed that SAEs were fully reported.
u. Only a summarized analysis of the events “dizziness”, “dry mouth”, “sweating”, “malaise” and “influenza like symptoms” was reported, provided they were assessed as severe by the investigator. Individual AEs were not analysed separately, irrespective of their severity.
v. Only AEs assessed by the investigator as moderate or severe are reported. All manifestations, even mild ones, are considered relevant for the side effects under consideration. However, these were not taken into account in the available analyses.
w. Data are only available for the placebo arm; no data on smokers with an event in the nicotine arm are available.

AE: adverse event; QoL: health-related quality of life; SAE: serious adverse event; PT: Preferred Term

Other morbidity outcomes

In 12 studies, results on other morbidity outcomes are available. In 6 manufacturer studies, symptoms associated with smoking (including cough, phlegm, changes in the sense of smell and taste, shortness of breath) were surveyed. In the EAGLES/CATS study, several instruments were used to analyse psychiatric symptoms such as anxiety, depression, or suicidality. In the T90NI01 study [280] and the Garvey 2000 study [200], the Profile of Mood States (POMS) instrument was used to record mood states. In the Hughes 2003 study [220], which included smokers with previous alcohol dependence, alcohol-related cravings were measured using visual analogue scales. The Positive and Negative Affect Schedule (PANAS) was used to record emotional states in the Jorenby 1999 study [224], which included smokers with a history of depression. Furthermore, various psychological variables were surveyed in the Prapavessis 2007 study. Overall, there is only a small amount of data on additional morbidity outcomes in the study pool for nicotine. It is not assumed that the evaluation of these limited data would have a relevant influence on the conclusion of the benefit assessment. Other morbidity outcomes are therefore not considered further in the present benefit assessment of nicotine.

Health-related quality of life

Health-related quality of life was assessed in 3 manufacturer studies using the original version of the Short Form-36 Health Survey (SF-36) and in 2 manufacturer studies using the SCQoL. In addition, in the Bolliger 2000 study [178], health-related quality of life was to be assessed using the SF-36, as stated in the publication. However, no results were reported. Instruments for recording health-related quality of life were therefore only used in individual studies in the study pool. It is not assumed that the evaluation of these limited data would have a relevant influence on the conclusion of the benefit assessment. The outcome “health-related quality of life” is therefore not considered further in the present benefit assessment on nicotine.

Side effects

Cardiovascular side effects

To ensure the patient relevance of the outcome “cardiovascular side effects”, this was defined as major adverse cardiovascular events (MACE) or cardiovascular SAEs e.g. operationalized as SAEs in the SOC “cardiac disorders”).

Information on SAEs in the SOC “cardiac disorders” or similar information (e.g. “cardiovascular disorders” according to the classification system of the World Health Organization [WHO]) is available for 10 of the 43 studies. Furthermore, as described in Section 4.4.2, MACE were reported in the EAGLES/CATS study. The definition of MACE+ used in the EAGLES/CATS study is considered sufficiently similar to an evaluation of cardiovascular SAEs, so that these two operationalizations are considered together in the present benefit assessment. Suitable data for the outcome “cardiovascular side effects” are thus available for a total of 11 studies. With the exception of the Joseph 1996 study, cardiovascular SAEs were either not reported in the

other studies or only lists of SAEs with individual details of each SAE were available, but not analyses of the number of smokers with SAEs in the SOC “cardiac disorders” or a comparable operationalization. The cardiovascular side effects were not extracted from the lists of SAEs. In the Joseph 1996 study, results were reported on a selection of different cardiovascular SAEs and death defined a priori. A complete analysis of all cardiovascular SAEs without considering non-cardiovascular deaths is not available. Therefore, no data suitable for the benefit assessment are available for the Joseph 1996 study.

Neuropsychiatric side effects

According to the SPC, neuropsychiatric side effects were mainly observed during treatment with varenicline (see Section 4.4). It is not to be expected that neuropsychiatric side effects will occur to any relevant extent during treatment with nicotine. Neuropsychiatric side effects are therefore not relevant for research question 4 and are not considered further in the following analyses.

Other specific adverse events

Complete data on all specific AEs analysed in the present benefit assessment are available for 18 of the 43 studies. For the study 94NNBT011 [153], suitable data are only missing for the outcome “irritations in the mouth and throat”. For 5 other studies, data are only available on individual specific AEs.

Data on specific AEs are only available for study 98-NNCG-017 [166] with regard to the frequency of events that occurred, but not on the number of smokers with an event. In study NICLIB-9142-001 [237], events for which a causal relationship with treatment was suspected were reported separately from events for which such a relationship was not suspected. For study T89NT07 [279], there are only separate data on specific side effects for which a causal relationship with the treatment was suspected, withdrawal symptoms, and intercurrent diseases. A summarized analysis of all specific AEs that occurred, regardless of whether there was a causal relationship with the treatment, was missing in both studies. A summarized analysis of all specific AEs in the studies T91NT08 [286], T93NNPA004 [292] and Tonnesen 2012 [293] was also missing. In study T91NT08, data on AEs were presented separately for withdrawal symptoms, systemic AEs, local AEs, intercurrent diseases, and other AEs that could not be assigned to the aforementioned categories. For study T93NNPA004, data on specific AEs are available for the first 8 weeks of treatment. However, treatment with nicotine was planned in the study for 12 weeks or 26 weeks, depending on the treatment arm. In addition, events that occurred during the follow-up period were presented separately in the study. In the Tonnesen 2012 study, only specific side effects with a suspected causal relationship to the treatment were reported. No data were reported for 13 additional studies, or the data reported on individual specific AEs were not suitable for the benefit assessment. Therefore, no (suitable) data on specific AEs are available for a total of 19 studies.

4.5.3 Assessment of the risk of bias of the results

A total of 43 studies were included in the analyses for the present benefit assessment of nicotine. Across outcomes, the results of 23 studies were assessed as having a high risk of bias because the information on randomization and/or allocation concealment was unclear, while the results of the remaining 20 studies were assessed as having a low risk of bias across outcomes.

In terms of outcome-specific risk of bias, only 6 and 4 of the total of 43 studies were rated as having a low risk of bias for the results of permanent freedom from smoking at month 6 and month 12, respectively. In 14 (at month 6) and 11 (at month 12) studies, the number of patients who discontinued the study was very high or not reported at the respective time point (see Section 4.5.4.2), which leads to a high risk of bias in the results. In 5 (at month 6) or 11 studies (at month 12) no (suitable) data were reported or the outcome was not recorded. The risk of bias in the results of the remaining 18 or 17 studies was already rated as high across outcomes.

The results of the outcome “all-cause mortality” were assessed in 2 studies with a low risk of bias. In 12 studies, the risk of bias of the results was classified as high due to high study discontinuation rates, in 7 studies due to a high risk of bias across outcomes. 22 studies reported no data or the outcome was not recorded.

For the overall rate of SAEs, 7 studies show a low risk of bias in the results. In 10 studies, the risk of bias of the results was already rated as high across outcomes, the results of 13 additional studies were rated with a high risk of bias due to high or unclear study discontinuation rates. 13 studies reported no (suitable) data.

The results of the outcome “cardiovascular side effects” were assessed in 3 studies with a low risk of bias. In 8 additional studies, the results were assessed as having a high risk of bias, either because the risk of bias at the study level was already high or there were high study discontinuation rates. The remaining 32 studies reported no suitable or usable data. For the remaining outcomes related to AEs, there are only 1 or 2 studies with a low risk of bias. Reasons for a high risk of bias in the results are primarily a high risk of bias across outcomes, high study discontinuation rates, and the lack of blinding with subjective outcome recording.

Detailed information on the risk of bias across outcomes and on the outcome-specific risk of bias can be found in Table 62 of the full report.

4.5.4 Results on patient-relevant outcomes

Potential evidence base given the available data

The evidence base was initially derived separately for each outcome according to the methodology described in the report plan (see sections A2.3.3 and A2.3.6) and in the General Methods 6.1 of the Institute [300]. As shown in Section 4.5.3 and in Table 62 of the full report, there are outcome-specific studies with high and low risk of bias in the results. The outcome-specific assessment of the risk of bias reveals a moderate or high certainty of results. Initially, only the studies with high qualitative certainty of results are considered. The conclusions about the evidence base derived from the studies with high qualitative certainty of results cannot be weakened by including the studies with moderate qualitative certainty of results, but rather enhanced. Furthermore, when deriving conclusions for the evidence base, the principles described in detail in the General Methods 6.1 of the Institute [300] apply.

As described in Section 4.5.1, the total population of the studies is used to assess the benefit of nicotine in comparison with no drug treatment for smoking cessation in smokers with severe tobacco dependence and is considered for all relevant outcomes. Since subgroup analyses according to FTCD cut-off values are only available for the outcome “permanent freedom from smoking”, which is relevant for the benefit assessment, conclusions on the benefit or harm of nicotine based on the total population for the other outcomes are subject to a higher degree of uncertainty. Due to this uncertainty, it cannot be clarified to the same extent for these outcomes whether there are potentially other or further advantages or disadvantages of nicotine for smokers with severe tobacco dependence in comparison with no drug treatment for smoking cessation. Therefore, the certainty of conclusions is downgraded for all outcomes with the exception of permanent freedom from smoking. Overall, on the basis of the available information for the outcome "permanent freedom from smoking", maximum proof, for example for a greater benefit, can be derived. For all other outcomes, on the other hand, no more than indications can be derived.

Subgroup characteristics and other effect modifiers

Subgroup analyses were conducted based on FTCD or FTQ cut-off values for the present benefit assessment to examine potential effect modification by the severity of tobacco dependence. As no relevant effect modification was shown here, the overall population is used for the benefit assessment (see Section 4.5.1).

According to the report plan, subgroup analyses by age (12 to 17 years/18 to 65 years/> 65 years), by sex, and by mental comorbidities were also planned. However, subgroup analyses according to these factors are generally not available in the studies on nicotine for the outcomes considered in the benefit assessment. The mean age of smokers in the 43 studies considered ranges between 31 and 61 years (see Table 31 and Table 34 of the full report). Data on the proportion of smokers aged > 65 years are not available for the vast majority of

studies. In studies on adolescent smokers, the outcome of permanent freedom from smoking was not recorded. As a result, these studies are not included in the analyses for the present benefit assessment (see Section 4.1). Overall, based on the available data, it is not possible to assess whether there was an effect modification by the characteristic of age. Based on the results on adolescent smokers from other systematic reviews, there are no signs of effect modification for this age group (see Section 4.1).

Three studies (NICLIB-9142-001, Pirie 1992, Prapavessis 2007), included only female smokers, while the studies CHN-Nicotine Mint Lozenge-002 and Abdelghany 2022, included almost exclusively male smokers. There were no systematic differences in the effects for the outcomes analysed between the studies that only included female smokers and the other studies (see Section A3.3.3).

Smokers with mental comorbidities were included in 1 of the 2 cohorts of the EAGLES/CATS study. There was no systematic difference in the effects between the EAGLES/CATS study and the other studies for any of the outcomes analysed.

While effect modifications for the subgroup characteristics defined in the report plan cannot be conclusively assessed in the present data situation, there are no signs overall that there is a relevant effect difference between the subgroups specified in the report plan. The evidence base is therefore derived based on the total population without taking into account subgroup characteristics.

4.5.4.1 Results on all-cause mortality

Suitable data for the outcome of all-cause mortality are available from 19 studies. In each case, the longest reported survey period was used for the benefit assessment. In most studies, the outcome was reported up to the end of the study. For 2 studies, data on overall mortality are only available up to the end of treatment. No statistically significant difference between the treatment groups was shown for the outcome of all-cause mortality (see Section A3.3.3.2). There is no hint of greater or lesser harm from nicotine in comparison with no drug treatment for smoking cessation.

4.5.4.2 Results on permanent freedom from smoking (at month 6 and at month 12)

As described in Section 4.1, only studies that have reported the outcome of permanent freedom from smoking at month 6 and/or month 12 were considered in the analyses. Data on permanent freedom from smoking at month 6 were not reported or were not usable in 5 studies. In 11 studies, no data were reported on permanent freedom from smoking at month 12. For permanent freedom from smoking at month 6, the studies with high certainty of results show a statistically significant difference between the treatment groups in favour of nicotine (see Section A3.3.3.3). There was no statistically significant difference in the studies

with high certainty of results for permanent freedom from smoking at month 12 (see Section A3.3.3.4). A meta-analytical summary of studies with high and moderate certainty of results was not meaningfully possible due to significant heterogeneity. Therefore, a qualitative summary of the results for permanent freedom from smoking was made at month 12. There are moderately conclusive effects to the advantage of nicotine. It cannot be ruled out that individual studies show no effect or even an effect to the detriment of the intervention. Therefore, the certainty of conclusions for permanent freedom from smoking is weakened towards month 12. This results in a proof of greater benefit with regard to permanent freedom from smoking at month 6 and a hint of greater benefit with regard to permanent freedom from smoking at month 12 for nicotine in comparison with no drug treatment for smoking cessation.

Sensitivity analyses for permanent freedom from smoking

Data on study discontinuations are available for all manufacturer studies. The proportion of smokers who discontinued the study prematurely was > 90% in some cases (see Section A3.2.3). It is not clear from the study documents when patients discontinued the study. Smokers who discontinued the study prematurely were rated as non-responders in the studies. For the majority of IITs, data on study discontinuations are missing. To investigate the potential impact of a high number of missing data due to high study discontinuation rates with subsequent non-responder imputation, sensitivity analyses were conducted for the key outcome of permanent freedom from smoking (at month 6 and month 12) (see Section A3.3.4). This involved a separate analysis of studies in which ≤ 50% of the included smokers discontinued the study prematurely, and studies in which > 50% of the smokers discontinued the study, as well as studies for which no information on patients who discontinued the study was available. These sensitivity analyses show no significant heterogeneity between the studies with high, low or unknown study discontinuation rates. It is therefore sufficiently ensured that the imputation method chosen in the studies does not lead to a bias in the results that is relevant to the conclusion.

4.5.4.3 Results on serious adverse events

Suitable data for the outcome of SAEs are available from 29 studies. In each case, the longest reported survey period was used for the benefit assessment. In 17 studies, data on SAEs are available up to the end of the study. In 12 studies, data are available up to the end of treatment at the latest. No statistically significant difference between the treatment groups was shown for the outcome of SAEs (see Section A3.3.3.5). There is no hint of greater or lesser harm from nicotine in comparison with no drug treatment for smoking cessation.

4.5.4.4 Results on discontinuation due to adverse events

Suitable data for the outcome “discontinuation due to AEs” are available from 33 studies. Data on discontinuations due to AEs clearly refer to treatment discontinuation in 10 studies. In these cases, the survey period corresponds to the respective treatment duration. For the other studies, it is unclear whether the data refer to study discontinuation or treatment discontinuation. For the outcome “discontinuation due to AEs”, the studies show a statistically significant difference between the treatment groups to the disadvantage of nicotine with high certainty of results (see Section A3.3.3.6). There is an indication of greater harm from nicotine in comparison with no drug treatment for smoking cessation.

4.5.4.5 Results on cardiovascular side effects

Suitable data for the outcome “cardiovascular side effects” are available from 11 studies. In each case, the longest reported survey period was used for the benefit assessment. In 4 studies, data on cardiovascular side effects are available up to the end of the study. In the other studies, information on cardiovascular side effects is either available up to the end of treatment at the latest or information on the survey period is missing. No statistically significant difference between the treatment groups was shown for the outcome “cardiovascular side effects” (see Section A3.3.3.7). There is no hint of greater or lesser harm from nicotine in comparison with no drug treatment for smoking cessation.

4.5.4.6 Results on specific adverse events

Information on specific AEs usable for the present benefit assessment was reported in 19 manufacturer studies. In the IITs, there is only sporadic usable information on specific AEs. In each case, the longest reported survey period was used for the benefit assessment. In most of the manufacturer's studies, specific AEs were reported up to the end of the study. The sporadic data available on specific AEs in IITs cover the period up to the end of the study or up to the end of treatment, depending on the study.

Dry mouth, fatigue, and rash

Suitable data for the outcome “dry mouth” are available from 20 studies, and for the outcomes “fatigue” and “rash” respectively from 19 studies each. There was no statistically significant difference between the treatment groups for the outcomes “dry mouth”, “fatigue” and “rash” (see sections A3.3.3.8, A3.3.3.9, A3.3.3.13). In each case, there is no hint of greater or lesser harm from nicotine in comparison with no drug treatment for smoking cessation.

Results on headaches

Suitable data for the outcome “headaches” are available from 21 studies. For the outcome “headaches”, the studies with high certainty of results show a statistically significant difference between the treatment groups to the disadvantage of nicotine (see

Section A3.3.3.10). There is an indication of greater harm from nicotine in comparison with no drug treatment for smoking cessation.

Results on nausea

Suitable data for the outcome “nausea” are available from 23 studies. For the outcome “nausea”, the studies with high certainty of results show a statistically significant difference between the treatment groups to the disadvantage of nicotine (see Section A3.3.3.11). There is an indication of greater harm from nicotine in comparison with no drug treatment for smoking cessation.

Results on itching

Suitable data for the outcome “itching” are available from 19 studies. For the outcome “itching”, a meta-analytical summary of the studies with high certainty of results was not meaningfully possible due to significant heterogeneity. The qualitative summary of the results on the outcome "itching" from the studies with high certainty of results shows no conclusive effects (see Section A3.3.3.12). The meta-analytical summary of studies with high and moderate certainty of results, on the other hand, reveals a statistically significant difference to the disadvantage of nicotine. Overall, there is a hint of greater harm from nicotine in comparison with no drug treatment for smoking cessation.

Results on irritations in the mouth and throat

Suitable data for the outcome “irritations in the mouth and throat” are available from 20 studies. For the outcome “irritations in the mouth and throat”, the studies show a statistically significant difference between the treatment groups to the disadvantage of nicotine with high certainty of results (see Section A3.3.3.14). There is an indication of greater harm from nicotine in comparison with no drug treatment for smoking cessation.

4.5.5 Overall evaluation of results

Evidence map

The following Table 6 shows the evidence map regarding patient-relevant outcomes.

Table 6: Evidence map for nicotine vs. no drug treatment regarding patient-relevant outcomes

Comparison / Outcome category / Outcome	Nicotine vs. no drug treatment
Mortality	
All-cause mortality	⇔
Morbidity	
Permanent freedom from smoking (at month 6)	⇑⇑
permanent freedom from smoking (at month 12)	⇗
Other morbidity outcomes	–
Health-related quality of life	–
Side effects	
SAEs	⇔
Discontinuation due to AEs	⇓
Cardiovascular side effects	(⇔)
Neuropsychiatric side effects	–[a]
Dry mouth	⇔
Fatigue	⇔
Headache	⇓
Nausea	⇓
Itching	⇘
Rash	⇔
Irritations in the mouth and throat	⇓

⇑⇑: Proof of (greater) benefit from nicotine vs. no drug treatment
⇓: Indication of (greater) harm from nicotine vs. no drug treatment
⇗: Hint of (greater) benefit from nicotine vs. no drug treatment
⇘: Hint of lesser benefit or hint of (greater) harm
⇔: No hint, indication, or proof; homogeneous result
(⇔): No hint, indication or proof, homogeneous result; the 95% confidence interval for the relative effect is so imprecise that neither halving nor doubling of the effect can be ruled out
-: No usable data reported
a. The outcome is not relevant for nicotine and is therefore not considered further for research question 4.

AE: adverse event; SAE: serious adverse event

Assessment of the volume of unpublished data

Out of the 43 studies considered, 24 were manufacturer studies. For 11 of the 24 manufacturer studies, only previously unpublished results from CSRs are available. No relevant studies without reported results were identified for the drug nicotine. Thus, for the present benefit assessment, there is no overall limitation of certainty of conclusions due to unpublished data.

Weighing of benefits versus harms

For the comparison of nicotine with no drug treatment for tobacco cessation in smokers with severe tobacco dependence, there is proof of a greater benefit of nicotine for permanent freedom from smoking at month 6 and a hint of a greater benefit of nicotine for permanent freedom from smoking at month 12 based on the available data. For the present benefit assessment, permanent freedom from smoking at month 6 is considered decisive. The advantage of nicotine in permanent freedom from smoking is offset by negative effects in individual specific AEs. For each of the outcomes “discontinuation due to AEs”, “headache”, “nausea”, and “irritation of the mouth and throat”, there is an indication of greater harm from nicotine in comparison with no drug treatment for smoking cessation. Furthermore, there is a hint of greater harm from nicotine for the outcome “itching”. However, no statistically significant differences are evident in the outcomes of all-cause mortality and SAEs. Overall, the results regarding specific AEs as well as the outcome “discontinuation due to AEs” do not call into question the advantage of nicotine that arises for the significant outcome of permanent freedom from smoking.

No suitable data were available for the assessment of the other morbidity outcomes or health-related quality of life. It is not assumed that these missing data have a relevant influence on the conclusion.

In summary, this provides proof of a greater benefit from nicotine for smokers with severe tobacco dependence in comparison with no drug treatment for smoking cessation.

5 Conclusion

For research question 1 on comparing bupropion to no drug therapy, 51 potentially relevant studies were identified. For research question 5, 5 relevant studies and 1 potentially relevant study were identified, each of which investigated bupropion in combination with nicotine or varenicline. Research questions 1 and 5 could not be finalised because the requested study documents for bupropion were not provided by the manufacturer. The necessary data could not be obtained through information retrieval from other sources. In addition, due to the manufacturer's failure to provide data, no subgroup analyses could be carried out with regard to the severity of tobacco dependence, so that an effect modification by the severity of tobacco dependence for the drug bupropion or combinations with bupropion in comparison with no drug treatment cannot be excluded with sufficient certainty. An assessment of bupropion (research question 1 and 5) for smokers with severe tobacco dependence is therefore not possible.

For research question 2 on cytisine, 3 relevant studies were identified. Since subgroup analyses regarding the severity of tobacco dependence are available only for the smallest of the 3 studies, an effect modification by the severity of tobacco dependence for the drug cytisine cannot be excluded with sufficient certainty. A benefit conclusion for comparing cytisine to no drug treatment for smoking cessation for smokers with severe tobacco dependence is not possible based on the overall population of the studies in the present data situation. To enable this assessment, subgroup analyses on the characteristic of severity of tobacco dependence for the outcome "freedom from smoking" must be presented for all 3 studies.

To answer research question 3 on varenicline, a total of 20 studies were analysed on the basis of the total population after sufficiently reliable exclusion of effect modification by the characteristic of severity of tobacco dependence. For the outcome of permanent freedom from smoking, based on the available data, both at month 6 and at month 12, there is proof of a greater benefit of varenicline in comparison with no drug treatment for smoking cessation. For the outcomes “neuropsychiatric side effects”, “fatigue”, and “nausea”, there are indications of greater harm from varenicline in comparison with no drug treatment for smoking cessation. For each of the outcomes “discontinuation due to adverse events”, “dry mouth”, and “headaches”, there is also a hint of greater harm from varenicline. For all other outcomes, there are no statistically significant differences between the treatment groups or there are no (suitable) data available. It should be noted that the results on outcomes in the category of side effects and mortality are subject to uncertainty due to the lack of subgroup analyses according to Fagerström Test for Cigarette Dependence (FTCD) cut-off values, which means that it remains unclear whether there are potentially other or further advantages or disadvantages for smokers with severe tobacco dependence. It should also be noted that particularly the analysis of neuropsychiatric side effects (e.g. sleep disorders, abnormal

dreams, irritability) could potentially also take withdrawal symptoms into account. In addition, adverse events were only recorded in the studies until shortly after the end of treatment. Overall, the disadvantages for individual outcomes in the side effects category and the uncertainties described do not call into question the benefit of varenicline for smokers with severe tobacco dependence, which is based on clear advantages in the key outcome of permanent freedom from smoking. In the overall assessment, there is proof of a greater benefit from varenicline in comparison with no drug treatment for smoking cessation.

A total of 43 studies were analysed to answer research question 4 on nicotine. From studies that have included pregnant smokers or adolescent smokers, no data on the outcome of permanent freedom from smoking in an operationalization suitable for benefit assessment are available. These studies were therefore not considered further in the analyses for the present benefit assessment. However, taking into account high-quality systematic reviews on these patient populations, it can be assumed that the results of the present benefit assessment are also transferable to these subpopulations. The benefit conclusion therefore refers to the entire population covered by the approval. An effect modification by the characteristic of severity of tobacco dependence can be excluded with sufficient certainty for nicotine. Based on the available data, the outcome for permanent freedom from smoking at month 6 provides proof of a greater benefit from nicotine, and for permanent freedom from smoking at month 12, there is a hint of a greater benefit from nicotine compared to no drug treatment for smoking cessation. For the present benefit assessment, permanent freedom from smoking at month 6 is considered decisive. On the other hand, for the outcomes “discontinuation due to adverse events”, “headache”, “nausea”, and “irritation of the mouth and throat”, there are indications of greater harm from nicotine in comparison with no drug therapy for tobacco cessation. Furthermore, the outcome “itching” provides a hint of greater harm from nicotine. For all other outcomes, there are no statistically significant differences between the treatment groups or there are no (suitable) data available. It should be noted that the results on outcomes in the category of side effects and mortality are subject to uncertainty due to the lack of subgroup analyses according to FTCD cut-off values, which means that it remains unclear whether there are potentially other or further advantages or disadvantages for smokers with severe tobacco dependence. The advantage of nicotine, which is shown for the decisive outcome of permanent freedom from smoking, is not called into question by the disadvantages in the outcome of discontinuation due to adverse events and the disadvantages of individual specific adverse events. This assessment remains valid despite the higher uncertainty regarding the results for the outcomes for which no subgroup analyses are available according to FTCD cut-off values, particularly due to the significant advantage in the relevant outcome of permanent freedom from smoking. In the overall assessment, there is proof of a greater benefit from nicotine in comparison with no drug treatment for smoking cessation.

Table 7 summarises the results of the benefit assessment of bupropion, cytisine, nicotine and varenicline for smoking cessation in severe tobacco dependence.

Table 7: Conclusion of the benefit assessment

Research question	**Therapeutic indication**	**Intervention**	**Comparator intervention**	**Conclusion**
1	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Bupropion	No drug treatment for smoking cessation[b]	No conclusion possible
2	Smokers aged ≥ 18 and ≤ 65 years[a] with severe tobacco dependence	Cytisine		No conclusion possible
3	Smokers aged ≥ 18 years[a] with severe tobacco dependence	Varenicline		Proof of greater benefit of varenicline versus the comparator intervention
4	Smokers aged ≥ 12 years[a] with severe tobacco dependence	Nicotine[c]		Proof of greater benefit of nicotine versus the comparator intervention
5	Smokers[d] with severe tobacco dependence	Various combinations of the drugs bupropion, cytisine, varenicline and nicotine		No conclusion possible

a. The age of the population of smokers to be considered is determined by the approval of the respective drugs.
b. This also includes the use of placebo in the context of placebo-controlled studies. If supportive measures or non-pharmacological methods (e.g. behavioural therapeutic interventions) were used in a study for smoking cessation, it is assumed that these are carried out equally among smokers in the intervention arm and those in the comparator arm.
c. Nicotine is authorised in various forms of administration. Not all forms of nicotine administration are authorised for adolescents aged ≥ 12 and < 18 years. Nicotine is the only approved drug that can also be used in pregnant women.
d. The inclusion criterion for the age of smokers is determined by the respective combinations of drugs, taking into account the respective approvals.

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Please see full final report for full reference list.

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The full report (German version) is published under
https://www.iqwig.de/en/projects/a22-34.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

Search for systematic reviews

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to May 03, 2022

The following filter was adopted:

- Systematic review: Wong [301] – High specificity strategy

#	Searches
1	exp Tobacco Smoking/
2	exp "Tobacco Use"/
3	(smoking or ((tobacco or nicotine) adj1 ("use" or dependenc* or addiction))).ti,ab.
4	or/1-3
5	(bupropion* or cytisine* or varenicline*).mp.
6	nicotine/ and (exp Smoking Cessation/ or ("drug therapy" or "therapeutic use" or therapy).fs.)
7	nicotine*.ti.
8	(nicotine adj2 (patch* or gum or nasal spray or lozenge* or tablet* or sublingual or inhal* or replacement)).ab,ti. or (nicotine adj3 therap*).ti,ab.
9	or/5-8
10	and/4,9
11	Cochrane database of systematic reviews.jn.
12	(search or MEDLINE or systematic review).tw.
13	meta analysis.pt.
14	or/11-13
15	14 not (exp animals/ not humans.sh.)
16	and/10,15
17	16 and (english or german or multilingual or undetermined).lg.
18	..l/ 17 yr=2015-Current

2. International HTA Database

Search interface: INAHTA

#	Searches
1	"Tobacco Use"[mhe]
2	(smoking OR ((tobacco OR nicotine) AND (use OR dependenc* OR addiction)))[Title] OR (smoking OR ((tobacco OR nicotine) AND (use OR dependenc* OR addiction)))[abs]
3	#2 OR #1
4	bupropion* OR cytisine* OR nicotine* OR varenicline*
5	#4 AND #3
6	* FROM 2015 TO 2022
7	#6 AND #5

Search for primary studies

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to August 23, 2022

The following filter was adopted:

- RCT: Lefebvre [302] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)

#	Searches
1	Smoking/
2	Tobacco Use Disorder/
3	(smoking or smokers).ti,ab.
4	or/1-3
5	(bupropion* or cytisine* or varenicline*).mp.
6	nicotine/ and ("administration & dosage" or "therapeutic use").fs.
7	(nicotine adj3 (chewing or gum* or inhaler* or lozenge* or patch* or polacrilex or replacement* or spray* or sublingual or transdermal)).ti,ab,kf.
8	or/5-7
9	randomized controlled trial.pt.
10	controlled clinical trial.pt.
11	(randomized or placebo or randomly).ab.
12	clinical trials as topic.sh.
13	trial.ti.
14	or/9-13

#	Searches
15	14 not (exp animals/ not humans.sh.)
16	and/4,8,15
17	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
18	hi.fs. or case report.mp.
19	or/17-18
20	16 not 19
21	20 and (english or german or multilingual or undetermined).lg.

Search interface: Ovid

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process, In-Data-Review & Other Non-Indexed Citations August 23, 2022

#	Searches
1	(smoking or smokers).ti,ab.
2	(bupropion* or cytisine* or varenicline*).mp.
3	(nicotine adj3 (chewing or gum* or inhaler* or lozenge* or patch* or polacrilex or replacement* or spray* or sublingual or transdermal)).ti,ab,kf.
4	or/2-3
5	(clinical trial* or random* or placebo).ti,ab.
6	trial.ti.
7	or/5-6
8	and/1,4,7
9	(animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
10	hi.fs. or case report.mp.
11	or/9-10
12	8 not 11
13	12 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2022 August 23

The following filter was adopted:

- RCT: Wong [301] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	exp smoking/
2	tobacco dependence/
3	(smoking or smokers).ti,ab.
4	or/1-3
5	(bupropion* or cytisine* or varenicline*).mp.
6	nicotine replacement therapy/ or nicotine gum/ or nicotine patch/ or nicotinic agent/ or nicotine lozenge/
7	nicotine/ and (chewing gum/ or transdermal patch/ or smoking cessation/)
8	(nicotine adj3 (chewing or gum* or inhaler* or lozenge* or patch* or polacrilex or replacement* or spray* or sublingual or transdermal)).mp.
9	or/5-8
10	(random* or double-blind*).tw.
11	placebo*.mp.
12	or/10-11
13	and/4,9,12
14	13 not medline.cr.
15	14 not (exp animal/ not exp human/)
16	15 not (Conference Abstract or Conference Review or Editorial).pt.
17	16 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 7 of 12, July 2022

#	Searches
#1	[mh ^"Smoking"]
#2	[mh ^"Tobacco Use Disorder"]
#3	(smoking or smokers):ti,ab
#4	#1 or #2 or #3
#5	(bupropion* or cytisine* or varenicline*):ti,ab,kw
#6	[mh ^"nicotine"] and [mh /ad,tu]
#7	(nicotine near/3 (chewing or gum* or inhaler* or lozenge* or patch* or polacrilex or replacement* or spray* or sublingual or transdermal)):ti,ab
#8	#5 or #6 or #7
#9	#4 and #8
#10	#9 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
#11	#10 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown)))
#12	#11 in Trials

A.2 Searches in study registries

ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Expert Search

Search strategy
(nicotine dependence OR AREA[ConditionSearch] (smoking OR smokers OR tobacco)) AND AREA[InterventionSearch] (bupropion OR cytisine OR varenicline OR nicotine AND (chewing OR gum OR inhaler OR lozenge OR patch OR polacrilex OR replacement OR spray OR sublingual OR transdermal)) AND AREA[Phase] EXPAND[Term] COVER[FullMatch] ("Phase 2" OR "Phase 3" OR "Phase 4" OR "Not Applicable")

2. EU Clinical Trials Register

Provider: European Medicines Agency

- URL: https://www.clinicaltrialsregister.eu/ctr-search/search
- Type of search: Basic Search

Search strategy
bupropion* OR cytisine* OR varenicline* OR (nicotine AND (chewing OR gum* OR inhaler* OR lozenge* OR patch* OR polacrilex OR replacement* OR spray* OR sublingual OR transdermal))

3. Clinical Trials Information System

Provider: European Medicines Agency

- URL: https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en
- Type of search: Basic Search

Search strategy
bupropion, cytisine, varenicline, nicotine [Contain any of these terms:]

4. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
((nicotine AND (addiction OR dependen*)) OR (smoking OR smokers OR tobacco)) AND (bupropion OR cytisine OR varenicline OR (nicotine AND (chewing OR gum* OR inhaler* OR lozenge* OR patch* OR polacrilex OR replacement* OR spray* OR sublingual OR transdermal)))

A.3 Further information sources and search techniques

G-BA website and IQWiG website

G-BA

URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/

Search terms
bupropion, varenicline, vareniclin, cytisine, cytisin
Nikotin, nicotine
Tabakentwöhnung, smoking cessation

IQWiG

URL: https://www.iqwig.de/projekte/projekte-und-ergebnisse/

Search terms
bupropion, varenicline, vareniclin, cytisine, cytisin
Nikotin, nicotine
Tabakentwöhnung, smoking cessation