Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: a systematic review and meta-analysis

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Abstract

Abstract conten**Background**: Smoking is a chronic disease and one of the main causes of years of life lost or years lived with disability and is considered worldwide the main cause of preventable death. **Aims:** To review the efficacy and safety of cytisine for smoking cessation**. Design:** were previously established (PROSPERO ID: **CRD42022296780);** an exhaustive search was carried out in different databases, identifying randomized controlled trials (RCTs). **Settings:** health centers of any level. **Participants:** persons of any age or gender, smokers. **Interventions:** cytisine at standard dosage versus placebo, varenicline, and nicotine replacement therapy (NRT). **Findings**: We identified **12 RCTs**. Eight RCTs compared cytisine to placebo at the standard dose (RR= 2.25, 95% CI 1.40 to 3.62; I^2= 90%). Following sensitivity analysis, we pooled the findings of five RCTs evidencing that cytisine is an effective treatment for smoking cessation, increasing the chances of quitting We pooled the findings of five RCTs which contributed to the primary analysis covering **2134** patients, **1099** of whom took cytisine, and indicates that cytisine at the standard dosage is an effective smoking cessation treatment that increases the chances of quitting compared to placebo (smoking cessation rate at longest follow-up: **RR= 3.46**, 95% CI **2.45 to 4.89**; participants = 2134; **I^2= 18%;** smoking cessation rate at least six months: **RR of 3.40 (95% CI 2.17 to 5.32)**; participants = 1938; I^2= 35%; *low-quality evidence*). We estimate an **NNT of 6.** Two trials compared the efficacy of cytisine **versus NRT** and the combination of both studies yields modest results in favor of cytisine. Three trials compared cytisine **versus varenicline**, without a clear benefit for cytisine. Meta-analyses of all **non-serious AEs** in the cytisine group **versus placebo** groups yielded a RR of **1.24** (**95% CI 1.11 to 1.39**; participants = 5895; studies = 8; I^2 = 0%; *high-quality evidence*). **Conclusions**: cytisine increased the chances of successful smoking cessation by more than three-fold compared with placebo. Cytisine had a benign safety profile, with no evidence of serious safety concerns. Limited evidence suggests that cytisine may be more effective than NRT, with modest cessation rates. [O1]

Author(s):
Question: Cytisine compared to placebo for smoking cessation
Setting:
Bibliography: De Santi O, Greco V, Orellana M, Di Niro CA. Evaluation of the effectiveness of cytisine for the treatment of smoking cessation: a systematic review and meta-analysis. Base de Datos Cochrane de Revisiones Sistemáticas [Año], Problema [Problema].

Certainty assessment							Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cytisine	placebo	Relative (95% CI)	Absolute (95% CI)		
Smoking cessation rate at longest follow-up												
5	randomised trials	not serious	not serious	not serious	very serious[a]	none	224/1099 (20.4%)	55/1035 (5.3%)	RR 3.75 (2.83 to 4.97)	80 fewer per 1000 (from 110 fewer to 50 fewer)	⊕⊕◯◯ Low	CRITICAL
Smoking cessation rate at least six months												
4	randomised trials	not serious	not serious	not serious	very serious[a]	none	208/1007 (20.7%)	49/931 (5.3%)	RR 3.80 (2.82 to 5.11)	70 fewer per 1000 (from 100 fewer to 40 fewer)	⊕⊕◯◯ Low	CRITICAL
Subgroup: Income level of study population - Cytisine in low-income and middle-income countries (LMICs)												
3	randomised trials	not serious	very serious[b]	not serious	very serious[a]	none	420/1406 (29.9%)	371/1395 (26.6%)	RR 1.13 (1.00 to 1.27)	35 more per 1000 (from 0 fewer to 72 more)	⊕◯◯◯ Very low	IMPORTANT
Subgroup: Income level of study population - Cytisine in upper/middle-high income countries (MHICs)												
3	randomised trials	not serious	not serious	not serious	very serious[a]	none	54/462 (11.7%)	21/474 (4.4%)	RR 2.73 (1.69 to 4.42)	77 more per 1000 (from 31 more to 152 more)	⊕⊕◯◯ Low	IMPORTANT
Subgroup: Cytisine with behavioral therapy												
4	randomised trials	not serious	not serious	not serious	very serious[a]	none	183/662 (27.6%)	42/600 (7.0%)	RR 3.81 (2.81 to 5.17)	197 more per 1000 (from 227 more to 292 more)	⊕⊕◯◯ Low	IMPORTANT
Subgroup: Cytisine with minimal behavioral therapy (brief advice).												
2	randomised trials	not serious	very serious[c]	not serious	very serious[a]	none	432/1609 (26.8%)	375/1603 (23.4%)	RR 1.15 (1.02 to 1.29)	35 more per 1000 (from 5 more to 68 more)	⊕◯◯◯ Very low	IMPORTANT
Incidence of Adverse Events (AEs)-Non serious AEs												
8	randomised trials	not serious	not serious	not serious	not serious	none	541/2981 (18.1%)	418/2914 (14.3%)	RR 1.24 (1.10 to 1.39)	34 more per 1000 (from 14 more to 56 more)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. The total number of events in each arm is less than 300, being insufficient to meet the OIS criteria.
b. Heterogeneity: Chi² = 4.00, df = 1 (P = 0.05); I² = 75%.
c. Heterogeneity: Chi² = 9.47, df = 1 (P = 0.002); I² = 89%.

Figure 1: This is a caption

Figures

Figure 2
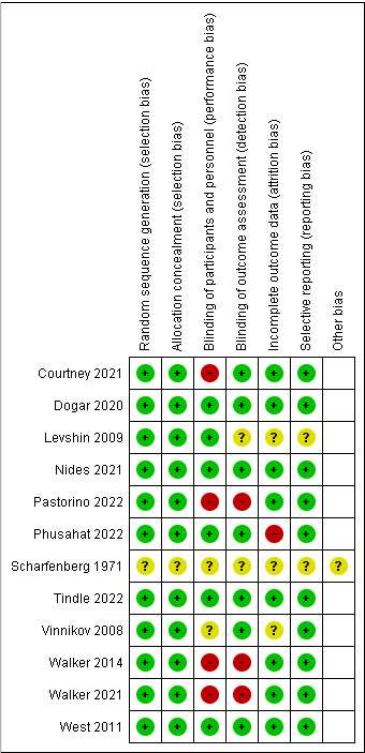
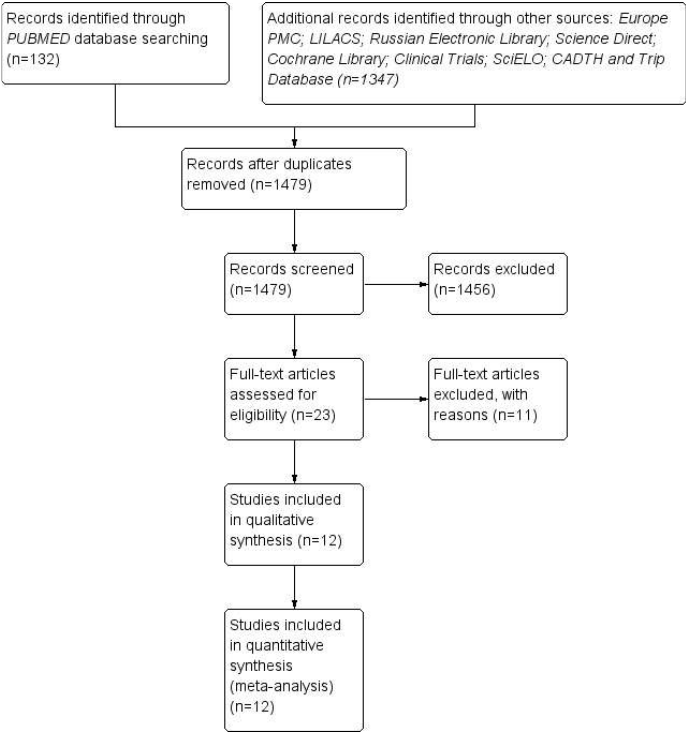Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

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Figure 2: This is a caption

Figures

Figure 1


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┌─────────────────────────────┐   ┌──────────────────────────────────────────────┐
│ Records identified through  │   │ Additional records identified through other    │
│ PUBMED database searching   │   │ sources: Europe PMC; LILACS; Russian Electronic │
│ (n=132)                     │   │ Library; Science Direct; Cochrane Library;      │
│                             │   │ Clinical Trials; SciELO; CADTH and Trip         │
│                             │   │ Database (n=1347)                               │
└─────────────────────────────┘   └──────────────────────────────────────────────┘

              ┌──────────────────────────────┐
              │ Records after duplicates     │
              │ removed (n=1479)             │
              └──────────────────────────────┘

        ┌──────────────────────┐         ┌──────────────────────┐
        │ Records screened     │────────▶│ Records excluded     │
        │ (n=1479)             │         │ (n=1456)             │
        └──────────────────────┘         └──────────────────────┘

        ┌──────────────────────┐         ┌──────────────────────┐
        │ Full-text articles   │────────▶│ Full-text articles   │
        │ assessed for         │         │ excluded, with       │
        │ eligibility (n=23)   │         │ reasons (n=11)       │
        └──────────────────────┘         └──────────────────────┘

        ┌──────────────────────┐
        │ Studies included     │
        │ in qualitative       │
        │ synthesis (n=12)     │
        └──────────────────────┘

        ┌──────────────────────┐
        │ Studies included     │
        │ in quantitative      │
        │ synthesis            │
        │ (meta-analysis)      │
        │ (n=12)               │
        └──────────────────────┘
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PRISMA study flow diagram.

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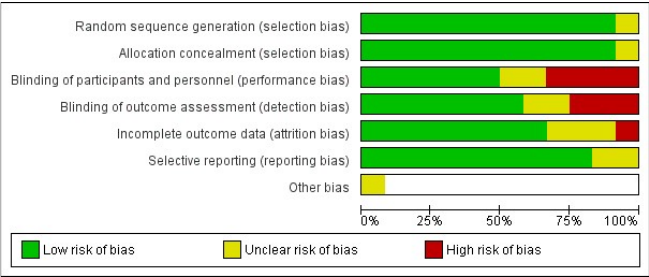Figure 3: This is a caption

[O1]Abstract according to requirements
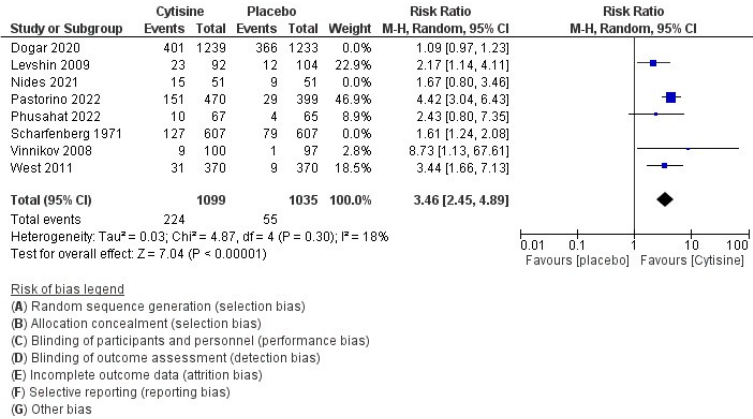
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Figures

Figure 3

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 4: This is a caption

6

Figures

Figure 4 (Analysis 1.1)

Study or Subgroup	Cytisine Events	Cytisine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Dogar 2020	401	1239	366	1233	0.0%	1.09 [0.97, 1.23]
Levshin 2009	23	92	12	104	22.9%	2.17 [1.14, 4.11]
Nides 2021	15	51	9	51	0.0%	1.67 [0.80, 3.46]
Pastorino 2022	151	470	29	399	46.9%	4.42 [3.04, 6.43]
Phusahat 2022	10	67	4	65	8.9%	2.43 [0.80, 7.35]
Scharfenberg 1971	127	607	79	607	0.0%	1.61 [1.24, 2.08]
Vinnikov 2008	9	100	1	97	2.8%	8.73 [1.13, 67.61]
West 2011	31	370	9	370	18.5%	3.44 [1.66, 7.13]
Total (95% CI)		**1099**		**1035**	**100.0%**	**3.46 [2.45, 4.89]**
Total events	224		55			

Heterogeneity: Tau² = 0.03; Chi² = 4.87, df = 4 (P = 0.30); I² = 18%
Test for overall effect: Z = 7.04 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI
0.01   0.1   1   10   100
Favours [placebo]   Favours [Cytisine]

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
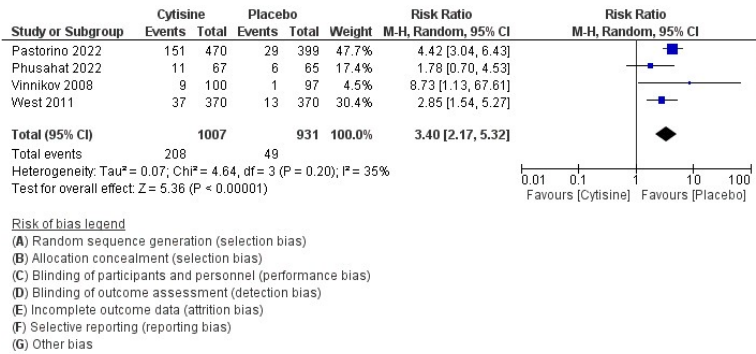**(F)** Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 1 Cytisine vs placebo, outcome: 1.1 Smoking cessation rate at longest follow-up.

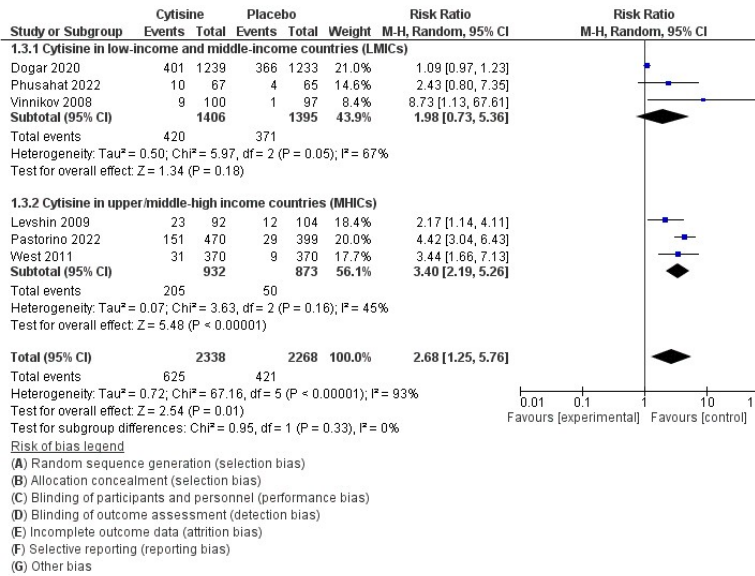Figure 5: This is a caption

Figures

Figure 5 (Analysis 1.2)

Forest plot of comparison: 1 Cytisine vs placebo, outcome: 1.2 Smokiing cessation rate at least six months.

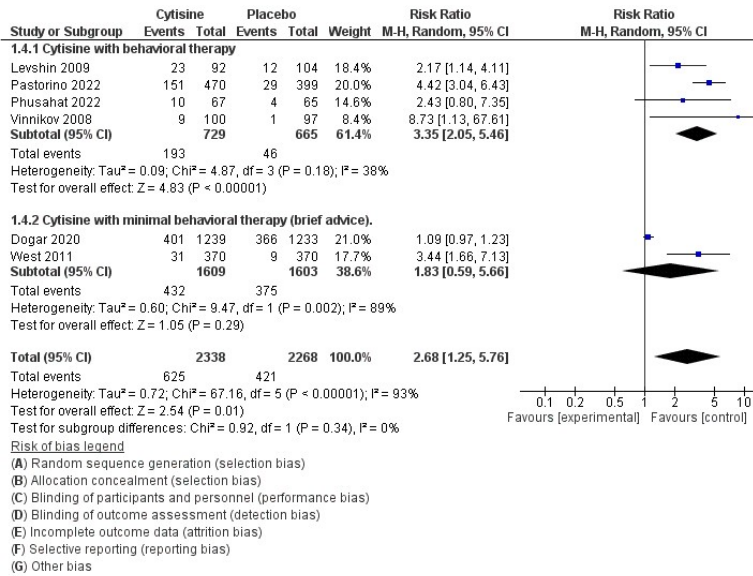Figure 6: This is a caption

Figures

Figure 6 (Analysis 1.3)

Forest plot of comparison: 1 Cytisine vs placebo, outcome: 1.3 Subgroup: Income level of study population.

Figure 7: This is a caption

Figures
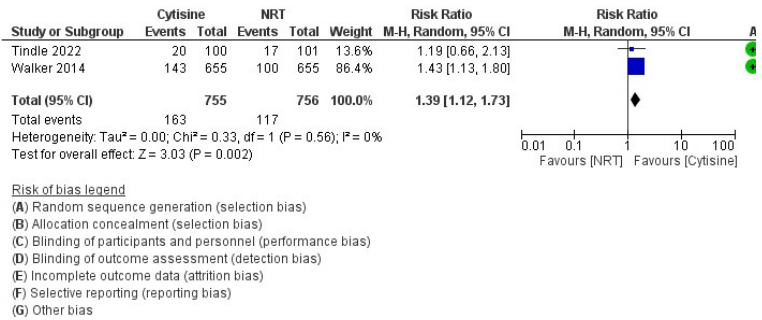
Figure 7 (Analysis 1.4)

Forest plot of comparison: 1 Cytisine vs placebo, outcome: 1.4 Subgroup: Cytisine in association with behavioral therapy.

Figure 8: This is a caption

Figures

Figure 8 (Analysis 2.1)

Study or Subgroup	Cytisine Events	Total	NRT Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Tindle 2022	20	100	17	101	13.6%	1.19 [0.66, 2.13]
Walker 2014	143	655	100	655	86.4%	1.43 [1.13, 1.80]
Total (95% CI)		755		756	100.0%	1.39 [1.12, 1.73]
Total events	163		117			

Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 3.03 (P = 0.002)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: 2 Cytisine vs NRT, outcome: 2.1 Smoking cessation rate at longest follow up.

Figure 9: This is a caption

Data and analyses
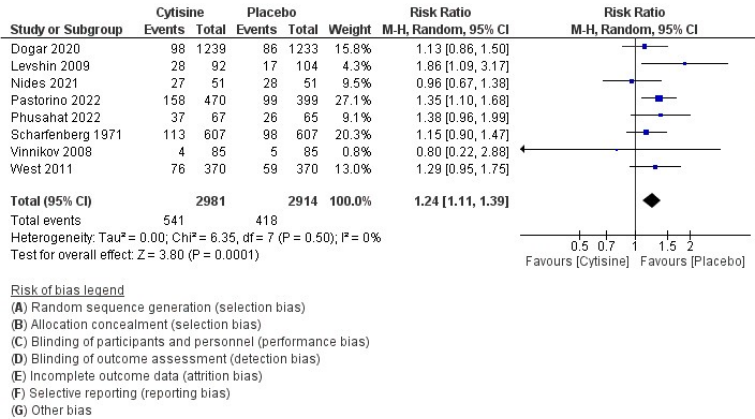
4 Incidence of Adverse Events (AEs)

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 All AEs in Cytisine vs placebo trials	8	5895	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.11, 1.39]

Figures

Figure 9 (Analysis 4.1)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Forest plot of comparison: Cytisine vs placebo, outcome 4.1. Incidence of non-serious AEs

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Figure 10: This is a caption

Hosted file

Cytisine for smoking cessation.docx available at https://authorea.com/users/581400/articles/621987-evaluation-of-the-effectiveness-of-cytisine-for-the-treatment-of-smoking-cessation-a-systematic-review-and-meta-analysis