Update Pharmakologie

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Agenda

1. Status quo in Cochrane Analysen bei zugelassenen Pharmakotherapien
2. Wirkungen und Nebenwirkungen in aktuellen Studien
3. Schwangerschaft und Pharmakotherapie
4. Gibt es Neues?

Cochrane Library

Cochrane Database of Systematic Reviews

Nicotine replacement therapy versus control for smoking cessation (Review)

Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T

Type of NRT	RR	95% CI	I^2	N of studies	N of participants Intervention/Control
Gum	1.49	1.40 to 1.60	40%	56*	10,596 / 11,985
Patch	1.64	1.53 to 1.75	24%	51	13,773 / 11,981
Inhalator	1.90	1.36 to 2.67	0%	4	490 / 486
Intranasal spray	2.02	1.49 to 2.73	0%	4	448 / 439
Tablets/lozenges	1.52	1.32 to 1.74	71%	8*	2326 / 2113
Oral spray	2.48	1.24 to 4.94	N/A	1	318 / 161
Choice of product	1.37	1.25 to 1.52	42%	7	4179 / 4109
Patch and inhalator	1.07	0.57 to 1.99	NA	1	136 / 109
Patch and lozenge	1.83	1.01 to 3.31	N/A	1	267 / 41
Patch and gum	1.15	0.64 to 2.06	50%	2	173 / 86
Patch, gum and lozenge	15.00	2.00 to 112.54	N/A	1	212 / 212

Wirksamkeit von Bupropion

Cochrane-Metaanalyse (Hughes et al., 2014)

Bupropion for smoking cessation						
Patient or population: people who smoke **Intervention:** bupropion						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Control	**Bupropion**				
Bupropion versus placebo/ control. Abstinence Follow-up: 6+ months	**115 per 1000**[1]	**187 per 1000** (172 to 203)	**RR 1.62** (1.49 to 1.76)	13728 (44 studies)	⊕⊕⊕⊕ **high**[2,3]	
Bupropion and NRT versus NRT alone. Abstinence Follow-up: 6+ months	**186 per 1000**[1]	**221 per 1000** (175 to 281)	**RR 1.19** (0.94 to 1.51)	3487 (12 studies)	⊕⊕◯◯ **low**[3,4,5]	
Bupropion versus NRT. Abstinence Follow-up: 6+ months	**254 per 1000**[1]	**244 per 1000** (216 to 277)	**RR 0.96** (0.85 to 1.09)	4086 (8 studies)	⊕⊕⊕◯ **moderate**[4]	

Wirksamkeit von Nikotinrezeptorpartialagonisten

Cochrane-Metaanalyse (Cahill et al., 2016)

Varenicline versus placebo or other first-line treatments for smoking cessation

Patient or population: Individuals who smoke tobacco
Setting: Varied
Intervention: Varenicline
Comparison: Varied controls

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Corresponding risk with varenicline				
Varenicline vs placebo: continuous/sustained abstinence at longest follow-up (24+ weeks)	Study population (where risk refers to quitt s)		RR 2.24 (2.06 to 2.43)	12,625 (27 RCTs)	⊕⊕⊕⊕ HIGH [1,2]	
	111 per 1000	250 per 1000 (230 to 271)				
Varenicline vs bupropion: continuous/sustained abstinence (24 weeks)	Study population (where risk refers to quitt s)		RR 1.39 (1.25 to 1.54)	5877 (5 RCTs)	⊕⊕⊕⊕ HIGH	
	171 per 1000	238 per 1000 (214 to 264)				
Varenicline vs NRT: point prevalence abstinence (24 weeks)	Study population (where risk refers to quitt s)		RR 1.25 (1.14 to 1 7)	6264 (8 RCTs)	⊕⊕⊕◯ MODERATE [3]	
	189 per 1000	237 per 1000 (216 to 259)				

Varenicline versus nicotine replacement therapy for long-term smoking cessation: an observational study using the Clinical Practice Research Datalink Davies et al., *Health Technology Assessment* Volume: 24, Issue: 9, Published in February 2020

Erfassung ab Sep 2006

N=220.136 aus UK

Effects of varenicline on smoking cessation, all-cause mortality and cause-specific mortality and hospitalisation for:
(1) chronic lung disease,
(2) lung cancer,
(3) coronary heart disease,
(4) pneumonia,
(5) cerebrovascular disease,
(6) diabetes, and
(7) external causes;

DOI: 10.3310/hta24090

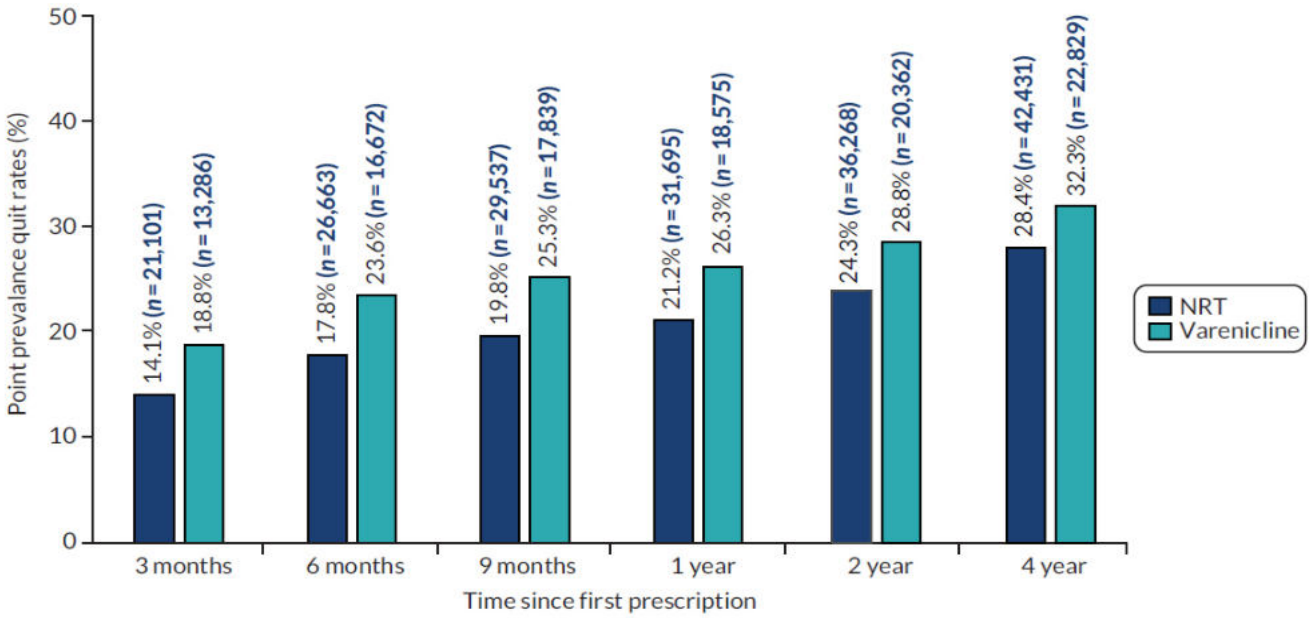

FIGURE 4 The proportion of patients who quit, by medication prescribed, at 3, 6 and 9 months and 1, 2 and 4 years after exposure ($n = 220,136$). Reproduced from Taylor *et al.*[17]

Varenicline versus nicotine replacement therapy for long-term smoking cessation: an observational study using the Clinical Practice Research Datalink

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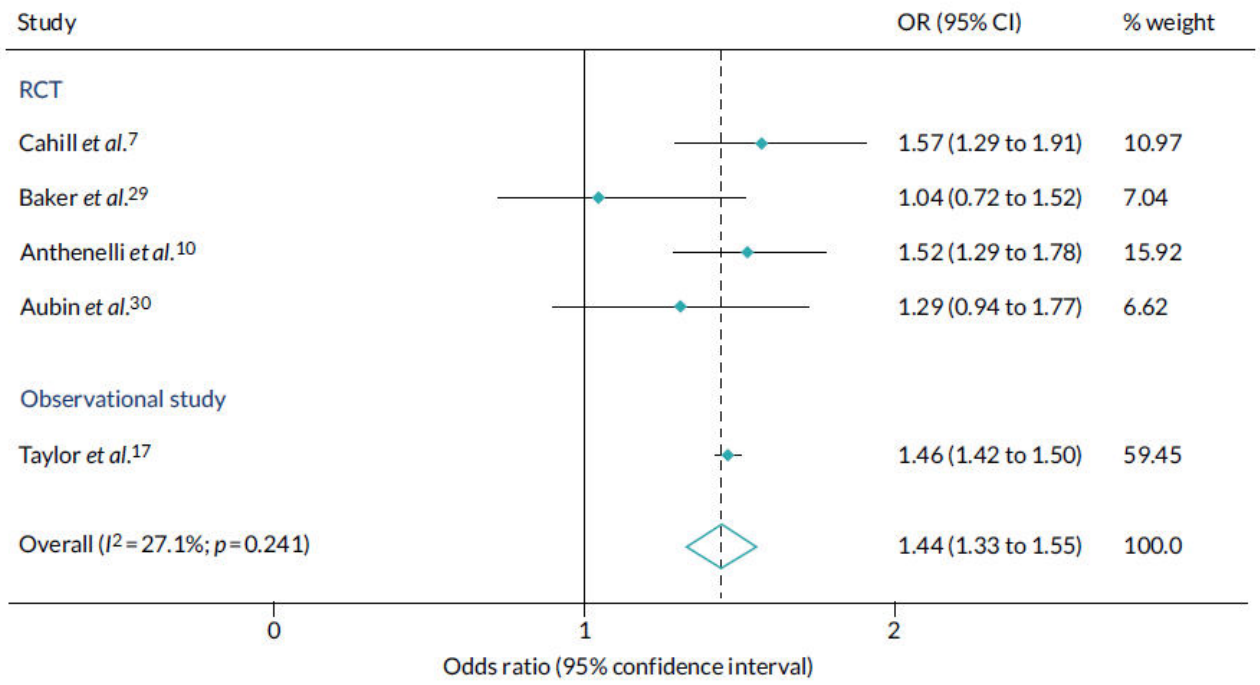


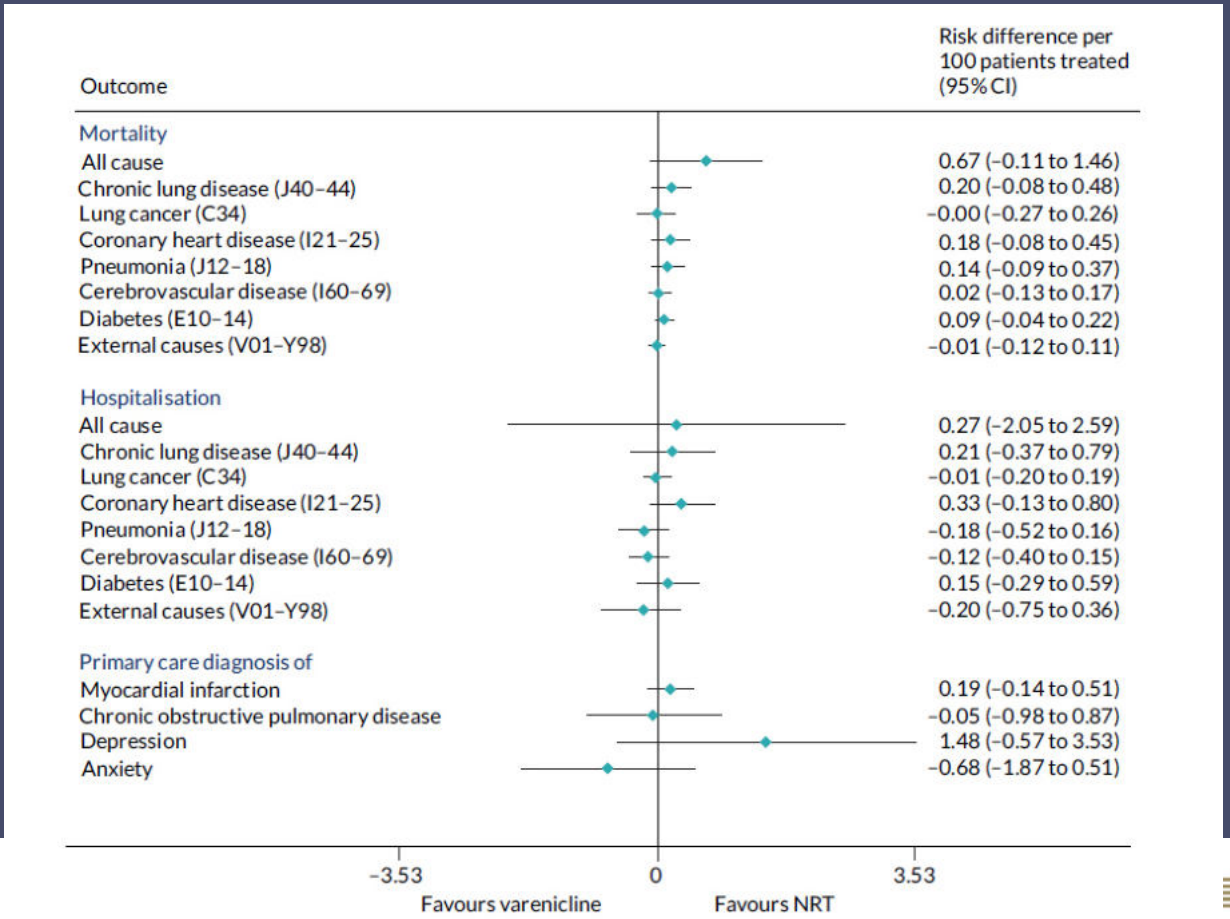
FIGURE 7 Random-effects meta-analysis comparing effect estimates (OR and 95% CI) from existing studies examining the effect of varenicline vs. NRT for smoking cessation at 6- to 12-month follow-up. Reproduced from Taylor *et al.*[17]

Varenicline versus nicotine replacement therapy for long-term smoking cessation: an observational study using the Clinical Practice Research Datalink

Davies et al., *Health Technology Assessment* Volume: 24, Issue: 9, Published in February 2020

"Effects of prescribing varenicline on longer-term health outcomes"

"Little evidence that patients prescribed varenicline had lower mortality 2 years after their first prescription risk difference: 0.67, (–0.11 to 1.46)"



Pharmacological interventions for promoting smoking cessation during pregnancy *Cochrane Systematic Review - Intervention Version published: 04 March 2020*

11 Studien mit 2412 Schwangeren

- 9 Studien mit NRT
- 2 Studien mit Bupropion
- 0 Studien mit Vareniclin oder E-Zigaretten

Pharmacological interventions for promoting smoking cessation during pregnancy *Cochrane Systematic Review - Intervention Version published: 04 March 2020*

NRT könnte bei schwangeren, rauchenden Frauen die Aufhörquoten in der Tabakentwöhnung erhöhen, vor allem in der Spätschwangerschaft (RR 1.37, 95% CI 1.08 to 1.74; I^2 = 34%, 9 studies, 2336 women).

Die Evidenz ist schwach, da der Effekt nicht stabil war, nachdem Studien mit einem potentiellen Bias sowie RCTs ohne eine Kontrollgruppe mit Placebo ausgeschlossen wurden

Keine Evidenz für positive oder negative Auswirkungen von NRT auf die Geburten

Keine Evidenz, dass Bupropion einen positiven Einfluss auf das Ergebnis einer Tabakentwöhnungsmaßnahme während der Schwangerschaft haben könnte (RR 0.74, 95% CI 0.21 to 2.64; I^2 = 0%, 2 studies, 76 women)

Health-care providers' concern regarding smoking cessation pharmacotherapies during pregnancy: Calls to a teratology information service. *Drug Alcohol Rev. 2020 Jan 26*

66 687 Anrufe bei MotherSafe zwischen 2001 und 2016

“Providers were more concerned about bupropion and varenicline than other medications within the same pregnancy risk categories. As this overestimation of risk may limit cessation pharmacotherapy use during pregnancy, research investigating strategies for correcting this imbalance is warranted.”

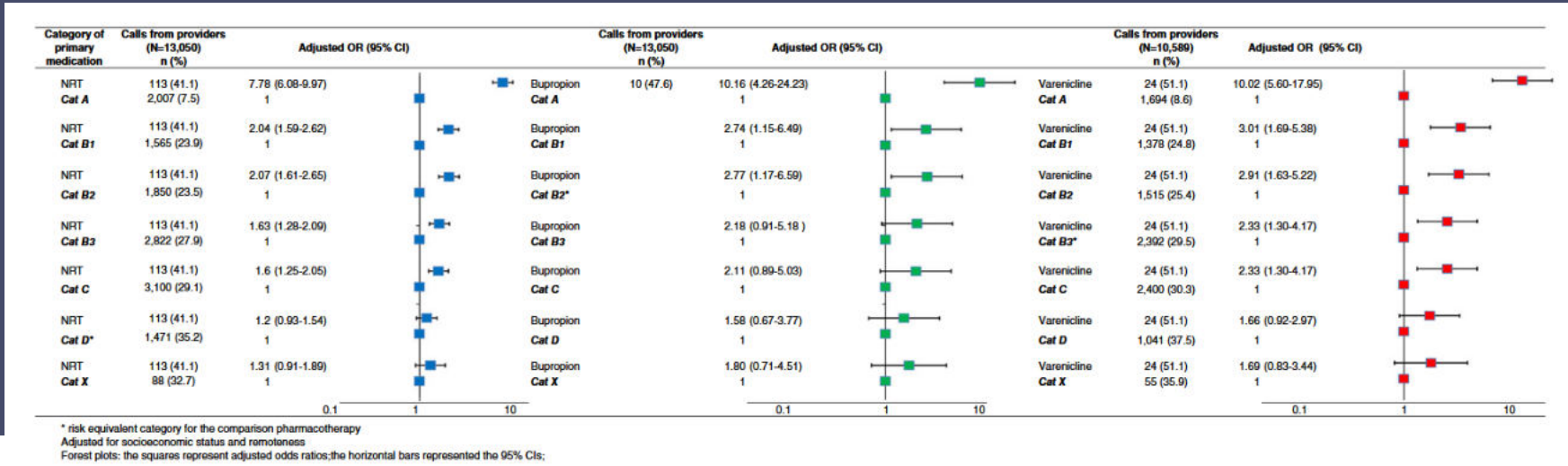
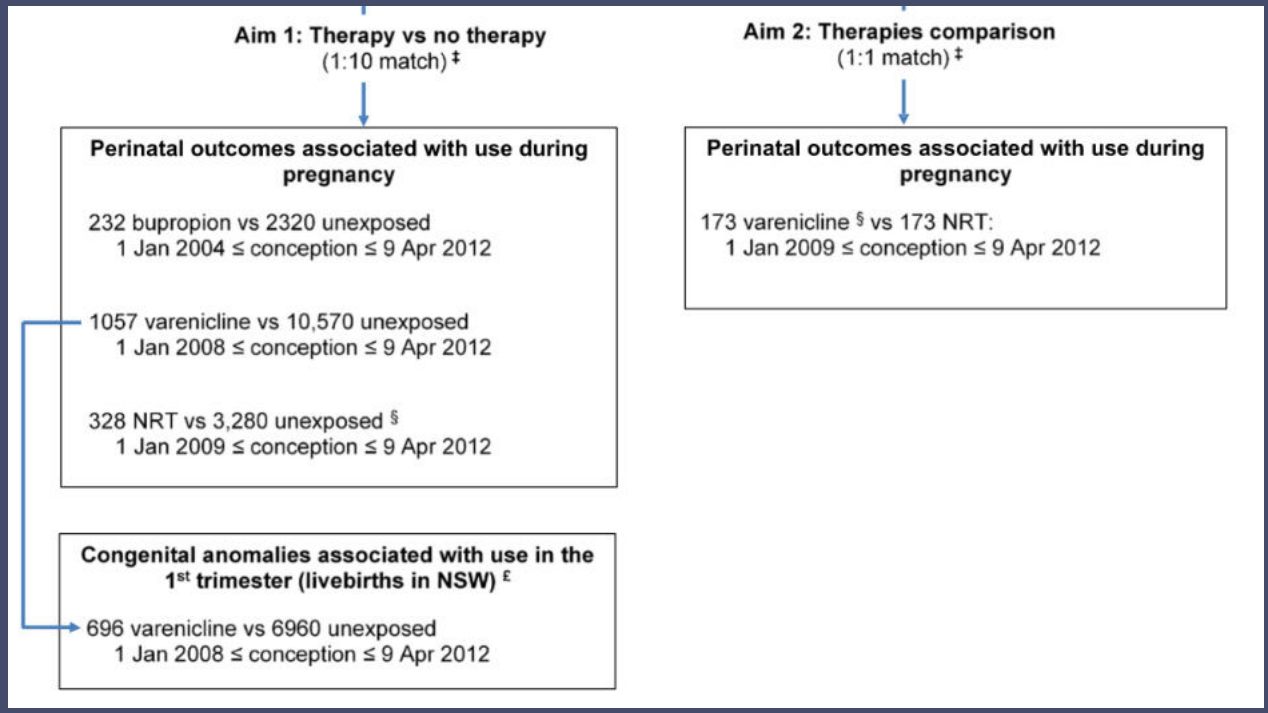


Figure 2 *Likelihood for calls regarding each pharmacotherapy to be from providers compared to other categories of medications, 2001–2016 (and 2008–2016 for varenicline).*

Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study *BMC Med. 2020; 18: 15. Published online 2020 Feb 5*

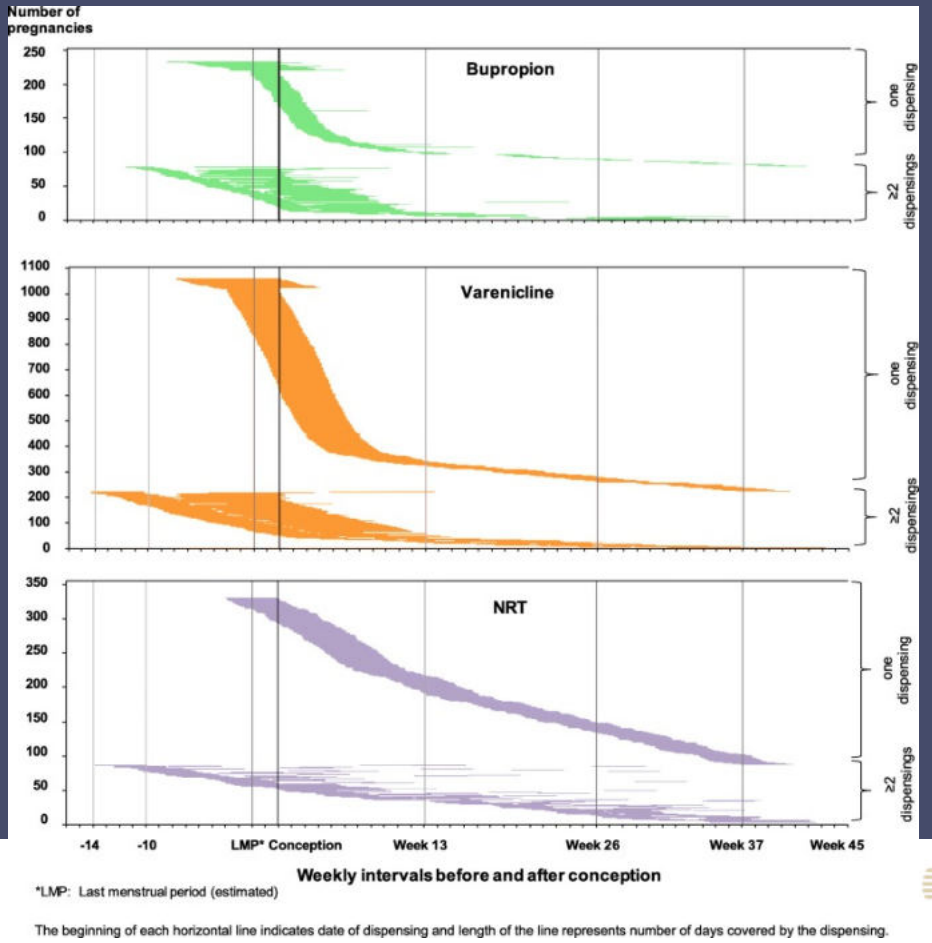
➔ Eine Exposition mit den untersuchten medikamentösen Unterstützungen bei einem Rauchstopp ist nicht mit einem erhöhten Risiko für Geburtskomplikationen verbunden.



Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study *BMC Med. 2020; 18: 15. Published online 2020 Feb 5*

Es findet sich sogar ein signifikant geringeres Risiko für perinatale Komplikationen bei einer Behandlung mit Vareniclin und auch kein erhöhtes Mißbildungsrisiko bei Einsatz von Vareniclin im ersten Trimester der Schwangerschaft

Kein significant erhöhtes Risiko für perinatale Komplikationen bei einer Behandlung mit Bupropion und NRT.



Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study *BMC Med. 2020; 18: 15. Published online 2020 Feb 5*

"Lower risk of adverse birth outcomes in varenicline-exposed pregnancies is inconsistent with recommendations that NRT be used in preference to varenicline."

Table 3 Major congenital anomalies in infants exposed to varenicline in the first trimester and matched comparison group. Data presented are numbers (percentage) of outcomes and hazard ratios (95% confidence interval)

	Varenicline, 1st trimester	Unexposed	Hazard ratio (95% CI)[†]
Any major congenital anomaly	20 (2.9%)	242 (3.5%)	0.91 (0.72–1.15)
Genitourinary	7 (1.0%)	67 (1.0%)	1.00 (0.67–1.51)
Cardiovascular	6 (0.9%)	52 (0.7%)	1.16 (0.75–1.79)
Musculoskeletal	< 5	57 (0.8%)	–
Gastrointestinal	< 5	28 (0.4%)	–
Nevers	< 5	18 (0.3%)	–
Respiratory	< 5	6 (0.1%)	–
Eyes	< 5	11 (0.2%)	–
Face, neck	0	< 5	–
Integumentary	0	< 5	–
Genetic syndromes	< 5	7 (0.1%)	–
Situs inversus	0	< 5	–
Others	< 5	9 (0.1%)	–

[†]Hazard ratio was obtained from the univariate model

Ganz neue Substanzen?

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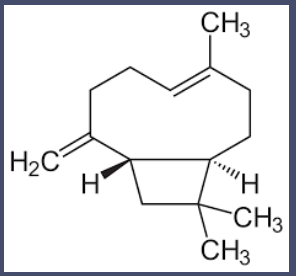
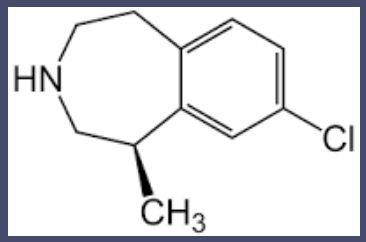
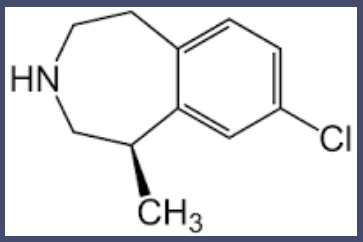


1. β-Caryophyllene (BCP): pflanzliches Terpenoid, Nahrungsergänzungsmittel, in Gewürznelken, Basilikum… erste Tierversuche
   Cannabinoid Receptor Agonist am CB2 Rezeptor, entzündungshemmend
   (He Y, Galaj E, Bi GH, Wang XF, Gardner E, Xi ZX. β-Caryophyllene, a dietary terpenoid, inhibits nicotine taking and nicotine seeking in rodents. Br J Pharmacol. 2019 Dec 27)
2. Lorcaserin: Serotonin 5-HT(2C) Agonist, Modulation des dopaminergen Belohnungssystems, zugelassen in USA zur Behandlung der Adipositas, in div. Phase II Prüfungen, randomisierte, placebo-kontrollierte Doppelblind-Studie
   (Higgins GA, Fletcher PJ, Shanahan WR. Lorcaserin: A review of its preclinical and clinical pharmacology and therapeutic potential. Pharmacol Ther. 2020)



Ganz neue Substanzen?



N=603, Beobachtungszeitpunkt: 12 Wochen

kontinuierliche Abstinenz (15,3% (20mg) vs. 5,6% (placebo), p=.0027)

Gewichtsveränderung bei kontinuierlich Abstinenten (-0,41kg vs. +0,73kg)

Häufigste Nebenwirkungen: Schwindel, Kopfschmerzen, Obstipation und Müdigkeit

Shanahan WR, Rose JE, Glicklich A, Stubbe S, Sanchez-Kam M (2017) Lorcaserin for Smoking Cessation and Associated Weight Gain: A Randomized 12-Week Clinical Trial. Nicotine & Tobacco Research, 2017, 944–951 doi:10.1093/ntr/ntw301

NEU: Rückzug der Substanz am 13.02.2020 wegen Hinweis der FDA auf Krebsrisiken

Laufende Studien: Clinical Trials (www.cliniclaltrials.gov)

Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation, Suspended, Terminated, Interventional Studies | smoking cessation | Adult | Phase Early Phase 1, 1, 2, 3 | Start date from 01/01/2010 to 01/01/2020

Gemfibrozil (N=1): Lipidsenker, erste positive Ergebnisse bei N=16 bzgl. CO in der Ausatemluft

Simvastatin (N=1): Lipidsenker, ohne Resultate

Guanfacin (N=1): Antihypertensivum, seit 2015 zugelassen als ADHS-Medikament bei therapieresistenten Jugendlichen, ohne Resultate

Meclizin (N=1): Antihistaminikum, geringe Effekte bei 25mg, nicht bei 50mg

Ganaxolon (N=1): Anxiolytikum, Antiepileptikum, N=16, bescheidene Resultate

Zonisamid (N=1): Antiepileptikum, kein Vorteil gegenüber Placebo

Memantin (N=1): NMDA-Antagonist, Antidementivum, kein Vorteil gegenüber Placebo

Laufende Studien: Clinical Trials

Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation, Suspended, Terminated, Interventional Studies | smoking cessation | Adult | Phase Early Phase 1, 1, 2, 3 | Start date from 01/01/2010 to 01/01/2020

Exenatid (N=2): Polypeptid aus dem Speichel der Krustenechse, Blutdrucksenker, noch ohne Resultate

Ramelteon (N=1): Schlafstörungen, verwandt mit Melatonin, N=69, 2019, kein Unterschied zu Placebo

Doxazosin (N=1): Antihypertensivum, auch in Traumabehandlung, nicht mehr im Handel in Deutschland, kein pos. Resultat bei 4 mg / 8 mg

D-Cycloserin (N=3): Antibiotikum bei Tuberkulose, auch als Add-on bei Angststörungen, Verhaltenstherapie, Wirkung über NMDA-Rezeptor, schwere toxische Nebenwirkungen

Cytisin versus Varenicline (N=2): laufende Studien a) seit 2017, 2140 Probanden, Auckland, b) am Start, N=380, Serbien

Zusammenfassung

1. **Zugelassen und wirksam: NRT, Bupropion und Vareniclin**
2. Langzeitauswirkungen von Vareniclin besser als bei NRT und nicht riskanter als NRT
3. NRT scheint auch in der Schwangerschaft ausreichend sicher zu sein
4. In der Schwangerschaft ist die Zurückhaltung gegenüber Medikamenten für die Tabakentwöhnung überproportional und unberechtigt hoch
5. Vareniclin scheint bei Schwangeren wirksam zu sein und weniger Nebenwirkungen aufzuweisen als keine Behandlung, auch NRT und Bupropion sind vermutlich ausreichend sicher
6. Etliche Studien zu alternativen Substanzen mit kleinsten Fallzahlen – spannend ist der Vergleich von Cytisin und Vareniclin, Lorcaserin ist out …

Vielen Dank für Ihre Aufmerksamkeit

Universitätsklinikum Tübingen