KÜSIMUS

Kas kasutada varenikliin või platseebo või bupropioon või NRT suitsetamise loobumise määra tõstmiseks?	
POPULATION:	suitsetamise loobumise määra tõstmiseks
INTERVENTION:	varenikliin
COMPARISON:	platseebo või bupropioon või NRT
MAIN OUTCOMES:	Varenikliin vs platseebo. Püsiv suitsetamisest loobumise määr; Varenikliin vs platseebo. A Suitsetamisest loobumise määr; Varenikliin vs platseebo. Abstinentsi saavutanud uuritavate arv pikima jälgimisperioodi lõpus; Varenikliin vs bupropioon. Suitsetamisest loobumise määr; Varenikliin vs bupropioon. Püsiv suitsetamisest loobumise määr; Varenikliin vs NRT. Abstinentsi saavutanud patsientide arv;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	

HINNANG

Problem
Is the problem a priority?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Suitsetamiset loobumisel võivad inimestel tekkida ebameeldivad aistingud ja tugev tung suitsetamise järele. Nikotiiniretseptorite agonistide (nt varenikliin) eesmärk on vähendada neid aistinguid ja naudingut, mida inimesed tavaliselt suitsetades kogevad (1) Varenikliin töötati välja 1997. aastal ja seda kirjeldatakse kui selektiivset nikotiiniretseptori agonisti (2). Varenikliini kasutamise kohta raseduse ajal pole piisavalt uuringuid. Keskmine hulk rasedate kohta saadud andmeid näitab, et varenikliin ei põhjusta väärarenguid ega avalda kahjulikku toimet lootele/vastsündinule. Loomkatsed on näidanud kahjulikku toimet reproduktiivsusele. Ei ole teada, kas varenikliin eritub inimese rinnapiima. Loomkatsed näitavad, et varenikliin eritub rinnapiima. Otsuse tegemisel, kas jätkata/katkestada rinnaga toitmine või jätkata/katkestada ravi CHAMPIX'iga, peab arvesse võtma rinnaga toitmise kasulikkust lapsele ja CHAMPIX-ravist saadavat kasu naisele. (Raviminfo)	

Ravijuhendites leidus järgmiseid soovitusi varenikliini kasutamise kohta suitsetamisest loobumise eesmärgil:

1. **US Preventive Services Task Force. Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons: US Preventive Services Task Force Recommendation. 2021** (3)

The USPSTF recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and US Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to nonpregnant adults who use tobacco.

• Convincing evidence that the benefit of behavioral interventions (including physician and nurse advice, individual and group counseling, and telephone and mobile phone–based interventions), alone or combined with pharmacotherapy, to increase achievement of tobacco smoking cessation in nonpregnant adults who smoke is substantial.

• Convincing evidence that the benefit of pharmacotherapy interventions, including nicotine replacement therapy (NRT), bupropion hydrochloride sustained-release (bupropion SR), and varenicline—with or without behavioral counseling interventions— to achieve tobacco smoking cessation in nonpregnant adults is substantial.

2. **Initiating Pharmacologic Treatment in Tobacco-Dependent Adults. American Thoracic Society. JAMA. 2021** (4)

● For tobacco-dependent adults in whom treatment is being initiated, we recommend varenicline over a nicotine patch (strong recommendation, moderate certainty in the estimated effects).

● For tobacco-dependent adults in whom treatment is being initiated, we recommend varenicline over bupropion (strong recommendation, moderate certainty in the estimated effects).

● For tobacco-dependent adults in whom treatment is being initiated, we suggest varenicline plus a nicotine patch over varenicline alone (conditional recommendation, low certainty in the estimated effects).

● For tobacco-dependent adults in whom treatment is being initiated, we suggest varenicline over electronic cigarettes

● In tobacco-dependent adults who are not ready to discontinue tobacco use, we recommend that clinicians begin treatment with varenicline rather than waiting until patients are ready to stop tobacco use (strong recommendation)

3. **Smoking Cessation, Version 1.2016, NCCN. Clinical Practice Guidelines in Oncology** (5)

● Combining pharmacologic therapy and behavior therapy is the most effective approach and leads to the best results for smoking cessation

○ the two most effective pharmacotherapy agents are combination nicotine replacement therapy (NRT) and varenicline

4. **NICE public health guidance update 2018** (6)

Ensure the following evidence-based interventions are available for adults who smoke:

● behavioural support (individual and group)

● bupropion[1]

● nicotine replacement therapy (NRT) – short and long acting

● varenicline[2]

● very brief advice. [2018]

1.3.3Offer varenicline as an option for adults who want to stop smoking, normally only as part of a programme of behavioural support, in line with NICE's technology appraisal guidance on varenicline. [2018]

1.3.4For adults, prescribe or provide varenicline, bupropion or NRT before they stop smoking. [2018]

1.3.5Agree a quit date set within the first 2 weeks of bupropion treatment and within the first 1 to 2 weeks of varenicline treatment. Reassess the person shortly before the prescription ends. [2018]

5. European Network for Smoking and Tobacco Prevention. Guidelines for Treating Tobacco Dependence. 2018. (7)

	Varenicline is a partial agonist of alpha4 beta2 nicotine receptor used as smoking cessation monotherapy with an efficacy versus placebo, which has been found to be greater than other first line monotherapies. Varenicline and combined high dose nicotine replacement therapy are equally effective.	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	27 uuringu põhjal (n=12 625) suurendas varenikliin püsiva suitsetamisest loobumise määra pikima jälgimisperioodi järel 11% võrra, tõstes suitsetamisest loobumise riski kaks korda platseeboga võrreldes (NNT ehk number needed to treat =9) 25 juhuslikustatud uuringu andmeil tõstis vareninkliin suitsetamisest loobumise määra 16% võrra kuue kuulise jälgimisperioodi järel (28.5% vs 12.4%), suurendades suitsetamisest loobumise riski üle kahe korra võrreldes platseeboga (RR 2.25) Pikima jälgimisperioodi jooksul saavutas varenikliini saanud patsientide seas abstinentsi peaaegu 17% rohkem uuritavaid vs kontrollrühmaga (4 RCT), tõstes abstinentsi saavutamise riski rohkem kui kolm korda (RR 3.64). Varenikliin vs bupropiooniga oli mõõdukalt efektiivsem suitsetamisest loobumisel, tõstes suitsetamiset loobumise riski keskmiselt 39% ning suitsetamisest loobunute arvu 6.7% 8 juhuslikustatud uuringu andmeil saavutas varenikliini saanud patsientide seas abstinentsi keskmiselt 5% rohkem uuritavaid võrreldes nikotiinasendusravi saanud rühmaga, tõstes abstinentsi saavutamise riski 6 kuu järel 25% (RR 1.25, 95%CI 1.14 - 1.37)	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Varenikliini kõige sagedasem kõrvaltoime on iiveldus, mis oli enamuse uuringute alusel kerge kuni mõõdukas ning möödus mõne aja jooksul pärast ravi alustamist. 29 juhuslikustatud uuringu anemete metaanalüüs näitas (n= 15 370), et varenikliin suurendab tõsise kõrvaltoimete riski keskmiselt 25% võrra (RR 1,25; 95% CI 1,04–1,49), sh tõsiste kardiaalsete kõrvaltoimete risk suureneb 36% võrra. Viimase puhul on tegemist statistiliselt ebaolulise tulemusega, mis kliiniliselt võib olla siiski oluline ja viitab kuni kahekordsele tõsiste kardiaalsete kõrvaltoimete riskile (RR 1.36, 95%CI 0.91 kuni 2.04). Siiski viitab usaldusvahemiku alumine piir sellele, et osades uuringutes esines kardiaalseid kõrvaltoimeid rohkem kontrollrühmas. NNH *(ingl.* number needed to harm) oli varenikliiniga ravi puhul siiski väga suur (NNH=166), viidates sellele, et ravi varenikliiniga on enamuse patsientide jaoks ohutu. Iiveldust esines varenikliini saanud patsientidel oluliselt rohkem vs platseebo saanutel (27.9% vs 8.5%) ning iiveldust esines keskmiselt igal 5-l ravi saanud patsiendil (NNH=5). Iivelduse tekkimise risk oli kolm korda suurem varenikliini saanud patsientide rühmas vs platseebo rühmaga. Unehäire tekkerisk oli 49% võrra kõrgem varenikliini saanud patsientidel (NNH=25). Unehäirega patsiente oli siiski ainult 4% võrra rohkem varenikliini saanute seas vs platseebo rühmas, st absoluutne erinevus ei olnud suur. Varenikliin tõstis mõnevõrra peavalu rsiki (RR 1.17, 95%CI 1.07 - 1.29), kuid ei mõjutanud depressiooni (RR 0.94, 95%CI 0.77 - 1.14) ega suitsiidaalse käitumise riksi (RR 0.68, 95% 0.43 - 1.07).	

Certainty of evidence

What is the overall certainty of the evidence of effects?		
JUDGEMENT	**TEADUSLIK TÕENDUSMATERJAL**	**TÄIENDAVAD KAALUTLUSED**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	Tõendusmaterjal baseerub Cochrane süstemaatilisel ülevaatel ja metaanalüüsil (39 RCT; n=25,290). Metaanalüüs näitas, et varenikliin on efektiivsem suitsetamise loobumise määra tõstmisel võrreldes pratseebo, nikotiinasendusravi ja bupropiooniga, tõstes suitsetamisest loobumise riksi vastavalt 124%, 39% ja 25%. Tõendatuse aste oli enamuse tulemusnäitajate jaoks mõõdukas, tõendatuse astet on langetatud nihke esinemise tõttu metaanalüüsi kaasatud uuringutes uuritavate randomiseerimise, pimendamise ja rühmadesse paigutamise strateegia puuduliku kirjelduse tõttu. Varenikliini platseeboga võrdlevates uuringutes esines suur statistiline heterogeensus, mida põhjustas üks suure väljalangenud uuritavate arvuga uuring. Uuringu eemaldamisel metaanalüüsist heterogeensuse näitaja (I2) langes 0% peale, viidates statistilise heterogeensuse puudumisele ning tõstes tõendatuse määra kõrge peale. Uuritavad olid enamasti täiskasvanud inimesed vanuses 40 kuni 50, aastat, meeste ja naiste osakaal oli peaaegu võrdne, suitsetatud sigarettide arv päevas vähemalt 18. Enamikus uuringutes said uuritavad 1 mg varenikliini kaks korda pöäevas 12 nädala jooksul. (1)	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	**TEADUSLIK TÕENDUSMATERJAL**	**TÄIENDAVAD KAALUTLUSED**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	**TEADUSLIK TÕENDUSMATERJAL**	**TÄIENDAVAD KAALUTLUSED**

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Sekkumisega saadud kasu kaalub kahju üles, kuid varenikliini kasutamisel suitsetamisest loobumisel peab arvestama raviga kaasnevate kõrvaltoimetega ning teavitama nendest patsienti.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Varenikliinile puudub käesoleval ajal Haigekassa poolne soodustus, seega raviga seotud kulu langeb täielikult patsiendi kanda. Soovitatav annus on 1 mg varenikliini kaks korda ööpäevas pärast 1-nädalast annuse tiitrimist vastavalt järgmisele skeemile: 1.-3. päev: 0,5 mg üks kord ööpäevas 4.-7. päev: 0,5 mg kaks korda ööpäevas 8. päev – ravi lõpuni: 1 mg kaks korda ööpäevas Patsient peaks kindlaks määrama suitsetamisest loobumise kuupäeva. CHAMPIX'i manustamist peab alustama tavaliselt 1...2 nädalat enne seda kuupäeva. CHAMPIX-ravi peab kestma 12 nädalat. Patsiendid, kes on 12 nädala lõppedes edukalt suitsetamisest loobunud, võib kaaluda täiendavat 12-nädalast ravikuuri CHAMPIX'iga annuses 1 mg kaks korda ööpäevas abstinentsi säilitamiseks (raviminfo) CHAMPIX TBL 1MG N14 + 0.5MG N11. 40.35eurot CHAMPIX TBL 1MG N28 45.19eurot	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED

○ Very low ○ Low ○ Moderate ○ High ● No included studies		

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	1) Hospitaliseeritud patsientide kohort: **Results:** At 2 years, there was a cost of $3,278 per additional person classified as an ex-smoker for the VT+C arm compared to the C arm. Incremental cost-effectiveness of hospital costs over a lifetime for VT+C compared to C was $26,688 per QALY. For the outcome of continuous abstinence at 12-months, the proportion of successful subjects in the VT+C arm was significantly greater with 31.1% (n=61) compared to 21.4% (n=42) in the QCA arm (RR 1.45, 95%CI 1.03 to 2.04, p=0.03). Statistical significance was maintained at 24 month follow-up (28.6 for VT+C group compared to 18.4% for QCA group; p=0.01). **Conclusion:** The trial effects modelled over a lifetime indicated that VT+C compared to C costs an estimated $28,688/QALY gained, which is cost-effective compared to many conventionally accepted therapies (8) 2) Compared with unaided cessation, counselling alone and other smoking cessation interventions, use of varenicline leads to an increased number of successful quitters. Varenicline is a very cost-effective intervention when compared with unaided cessation, with an incremental cost of 1656 eurit/QALY gained. Compared with brief counselling alone, varenicline is even more cost effective with a cost/QALY of only 240 eurot. When compared with bupropion and NRT, varenicline is a dominant alternative (cost saving and leading to better health). Although varenicline treatment is more expensive than bupropion treatment or NRT, it is dominant compared with those two alternative interventions. Compared with unaided cessation, varenicline enables avoiding 29.2 smoking-related diseases per 1000 smokers willing to quit. The disease that is most avoided by smoking cessation is COPD (65%), followed by CHD (16%), lung cancer (14%) and stroke (5%). A reduced incidence of smoking-related diseases will result in a decreased mortality. Compared with unaided cessation, varenicline prevents 1825 deaths in the considered cohort (n = 185 232), that is, 9.9 per 1000.	

Relative risks (RRs) of developing a smoking-related disease in the 35- to 64-year age group (9)

Morbidity RR in smokers RR in former smokers RR in never smokers

COPD

- Males 10.8 7.8 1.0

- Females 12.3 8.9 1.0

Lung cancer

- Males 21.3 8.3 1.0

- Females 12.5 4.8 1.0

CHD

- Males 2.6 1.6 1.0

- Females 3.2 1.4 1.0

Stroke

- Males 2.4 1 1.0

- Females 3.8 1.5 1.0

Equity
What would be the impact on health equity?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Võrdsust ja ebavõrdsust võib mõjutada ravimi kopsakas hind	

Acceptability
Is the intervention acceptable to key interest-holders?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	TEADUSLIK TÕENDUSMATERJAL	TÄIENDAVAD KAALUTLUSED
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Nikotiinasendusravi ja ravi varenikliiniga on võimalik Eestis rakendada nii perearstiabis, kui ka suitsetamisest loobumise kabinettides ja eriarstiabis.	

OTSUSTE KOKKUVÕTE

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know

	JUDGEMENT						
UNDESIRABLE EFFECTS	Large	**Moderate**	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	**Moderate costs**	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

VIIDETE KOKKUVÕTE

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