Snus som røykeavvenningsmiddel

Notat fra Kunnskapssenteret
Systematisk litteratursøk med sortering
September 2012

kunnskapssenteret

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Notat: ISBN 978-82-8121-487-3

September 2012

kunnskapssenteret

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ISBN 978-82-8121-487-3
Notat 2012
Publikasjonstype Systematisk litteratursøk med sortering
Antall sider 16 (19 inklusiv vedlegg)
Oppdragsgiver Helsedirektoratet
Emneord(MeSH) Smokeless tobacco, tobacco use cessation
Sitering Sæterdal I, Harboe I, Ringerike T, Klemp M. Snus som røykeavvenningsmiddel – systematisk litteratursøk med sortering. Notat 2012. Oslo: Nasjonalt kunnskapssenter for helsetjenesten, 2012.

Nasjonalt kunnskapssenter for helsetjenesten fremskaffer og formidler kunnskap om effekt av metoder, virkemidler og tiltak og om kvalitet innen alle deler av helsetjenesten. Målet er å bidra til gode beslutninger slik at brukerne får best mulig helsetjenester. Kunnskapsenteret er formelt et forvaltningsorgan under Helsedirektoratet, men har ingen myndighetsfunksjoner og kan ikke instrueres i faglige spørsmål.

Nasjonalt kunnskapssenter for helsetjenesten
Oslo, september 2012

Hovedfunn

Nasjonalt kunnskapssenter for helsetjenesten fikk i oppdrag av Helsedirektoratet å identifisere forskningslitteratur om effekt av snus som røykeavvenningsmiddel. Vi løste oppdraget ved å utføre et systematisk litteratursøk med påfølgende sortering av mulig relevante publikasjoner.

Metode

Vi utarbeidet søkestrategi for et systematisk litteratursøk om effekt av snus som røykeavvenningsmiddel. Det ble søkt i medisinske databaser etter systematiske oversikter og randomiserte kontrollerte studier. Søket ble utført i juni 2012. Minst to forskere gikk uavhengig av hverandre gjennom identifiserte referanser og vurderte relevans i forhold til inklusjonskriteriene.

Resultater

- Søket identifiserte totalt 909 referanser. Av disse var det 3 mulig relevante systematiske oversikter og 15 mulig relevante randomiserte kontrollerte studier. Vi har ikke undersøkt om de identifiserte studiene er inkludert i de systematiske oversiktene.
- Vi har presentert referanselister med tittel og sammendrag for den identifiserte forskningslitteraturen.

Tittel:

Snus som røykeavvennings-middel

Publikasjonstype:

Systematisk litteratursøk med sortering

Systematisk litteratursøk med sortering er resultatet av å
- søke etter relevant litteratur ifølge en søkestrategi og
- eventuelt sortere denne litteraturen i grupper presentert med referanser og vanligvis sammendrag

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Svarer ikke på alt:

- Ingen kritisk vurdering av studienes kvalitet
- Ingen analyse eller sammenfatning av studiene
- Ingen anbefalinger

Hvem står bak denne publikasjonen?

Kunnskapssenteret har gjennomført oppdraget etter forespørsel fra Helsedirektoratet

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Når ble litteratursøket utført?

Søk etter studier ble avsluttet juni 2012

Innhold

Forord

Nasjonalt kunnskapssenter for helsetjenesten fikk i oppdrag fra Helsedirektoratet å finne litteratur om effekt av snus som røykeavvenningsmiddel og effekt av ulike snusavvenningstiltak. Vi har besvart bestillingen med to notater; et systematisk litteratursøk med sortering for hver problemstilling. Dette notatet handler om å bruke snus som røykeavvenningsmiddel. Litteraturen i vår referanseliste kan utgjøre et relevant dokumentasjonsgrunnlag når Helsedirektoratet skal gi anbefalinger om røykesluttiltak.

Prosjektgruppen har bestått av:

- Ingrid Harboe, forskningsbibliotekar, Kunnskapssenteret
- Tove Ringerike, forsker, Kunnskapssenteret
- Ingvil Sæterdal, forsker, Kunnskapssenteret

Gro Jamtvedt	Marianne Klemp	Ingvil Sæterdal
Avdelingsdirektør	*Forskningsleder*	*Prosjektleder*

Innledning

Styrker og svakheter ved litteratursøk med sortering

Kunnskapssenterets produkt, litteratursøk med sortering blir utført ved at vi gjennomfører systematiske litteratursøk for en gitt problemstilling. Resultatene fra søket blir i sin helhet overlevert oppdragsgiver, eller vi kan gjennomgå søkeresultatet før overleveringen og sortere ut ikke-relevante artikler slik vi har gjort det i dette notatet. Dette gjøres basert på tittel og eventuelt sammendrag. Artiklene innhentes ikke i fulltekst. Dette gjør at vi kan ha inkludert titler som ville vist seg ikke å være relevante ved gjennomlesning av fulltekst. Vi benytter kun databaser for identifisering av litteratur og kan derfor ha gått glipp av potensielt relevante studier. Andre måter å identifisere studier på, som søk i referanselister, kontakt med eksperter på fagfeltet og upublisert litteratur, er ikke utført i dette oppdraget. Vi gjennomfører ingen kvalitetsvurdering av artiklene.

Ved en full kunnskapsoppsummering ville vi ha innhentet artiklene i fulltekst for endelig vurdering opp mot inklusjonskritene. Inkluderte studier ville så blitt kvalitetsvurdert i henhold til våre sjekklister og resultater sammenstilt, gradert og diskutert.

Begrunnelse for valg av søkestrategi

Vi har lagt bestillingen fra Helsedirektoratet til grunn for valg av søkestrategi. Bestillingen inneholdt to problemstillinger: i) Effekt av snus som røykeavvenningsmiddel og ii) Effekt av snusavvenningstiltak. Vi har laget en søkestrategi som omfatter begge problemstillinger. Vi har søkt i relevante elektroniske kilder, men ikke etter grå litteratur eller liknende. Vi har søkt etter systematiske oversikter og etter randomiserte kontrollerte studier. Vi har ikke gjennomgått de systematiske studienes referanselister. Noen av de randomiserte kontrollerte studiene kan derfor være inkludert i de systematiske oversiktene. Ved en fullstendig kunnskapsoppsummering ville vi ha inkludert systematiske oversikter først, og bare søkt etter primærstudier dersom de systematiske oversiktene ikke besvarte våre problemstillinger, eller for å oppdatere oversikten. For problemstillingen i dette notatet anså vi det som mest hensiktsmessig å utføre søkene samtidig.

Problemstilling

I dette notatet har vi søkt etter litteratur for følgende problemstilling:
Vil snus være et effektivt røykeavvenningsmiddel for folk som røyker?

Vi vil utarbeide et eget notat der vi presenterer litteraturlister for problemstillingen om effekt av ulike snusavvenningstiltak.

Metode

Litteratursøking

Vi søkte systematisk etter systematiske oversikter og/eller randomiserte kontrollerte studier i følgende databaser:

- Embase (Ovid) 1980 to 2012 Week 24
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
- PsycINFO 1987 to June Week 2 2012
- Cochrane Library: Cochrane Database of Systematic Reviews
  Cochrane Central Register of Controlled Trials
  Health Technology Assessment Database
- Centre for Reviews and Dissemination DARE (Database of Abstracts of Reviews of Effects)
- Web of Science (i Web of Knowledge)
- SveMed+
- PubMed

Forskningsbibliotekar Ingrid Harboe planla og utførte samtlige søk. Den fullstendige søkestrategien er vist i vedlegg til denne rapporten. Søk etter litteratur ble avsluttet i juni 2012.

Vi la bestillingen til grunn da vi utarbeidet litteratursøket. Bestillingen inneholdt to problemstillinger og vi søkte etter referanser som oppfylte våre inklusjonskriterier for populasjon, intervensjon og studiedesign for begge problemstillingene under ett. Vi sorterte deretter referansene basert på inklusjonskriteriene for hver problemstilling.

Inklusjonskriterier

Populasjon:	Personer som røyker
Tiltak:	Bruk av snus som røykeavvenningsmiddel
Sammenlikning:	Alle andre røykeavvenningsmidler/metoder, placebo

Studiedesign	Systematiske oversikter, randomiserte kontrollerte studier
Språk:	Vi hadde ingen språkbegrensinger i litteratursøket

Artikkelutvelging

To forskere (TR og IS) gikk gjennom alle titler og sammendrag for å vurdere relevans i henhold til inklusjonskriteriene. Vurderingene gjorde vi uavhengig av hverandre og sammenlignet i etterkant. Der det var uenighet om vurderingene, ble inklusjon eller eksklusjon avgjort ved konsensus.

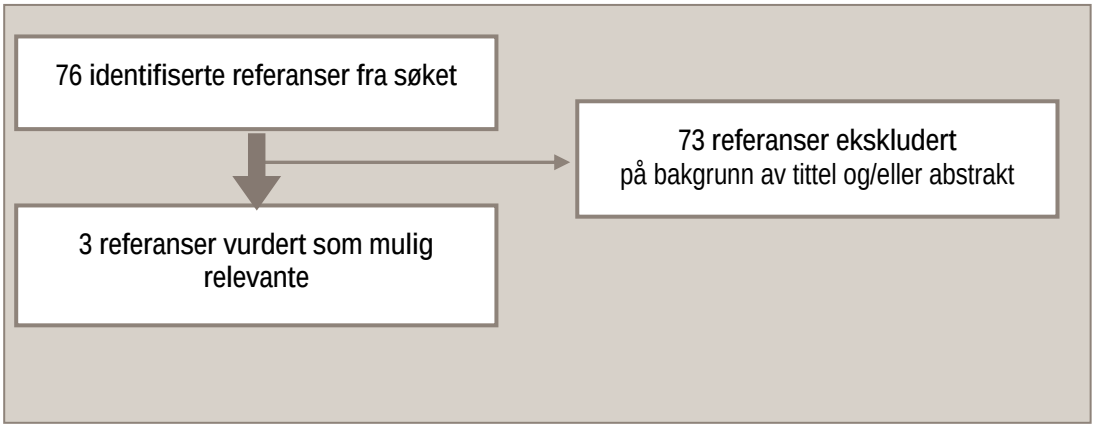
Utvelging av litteratur ble kun gjort basert på tittel og sammendrag. Vi bestilte ikke artiklene i fulltekst.

Resultat

Litteratursøk etter systematiske oversikter

Litteratursøket etter systematiske oversikter resulterte i 76 referanser. Vi vurderte tre av de identifiserte referansene til å være mulig relevante i henhold til inklusjonskriteriene, figur 1.

Hovedårsaken til eksklusjon var at publikasjonen omhandlet ulike tobakkavvenningstiltak og ikke snus som røykeavvenningstiltak.

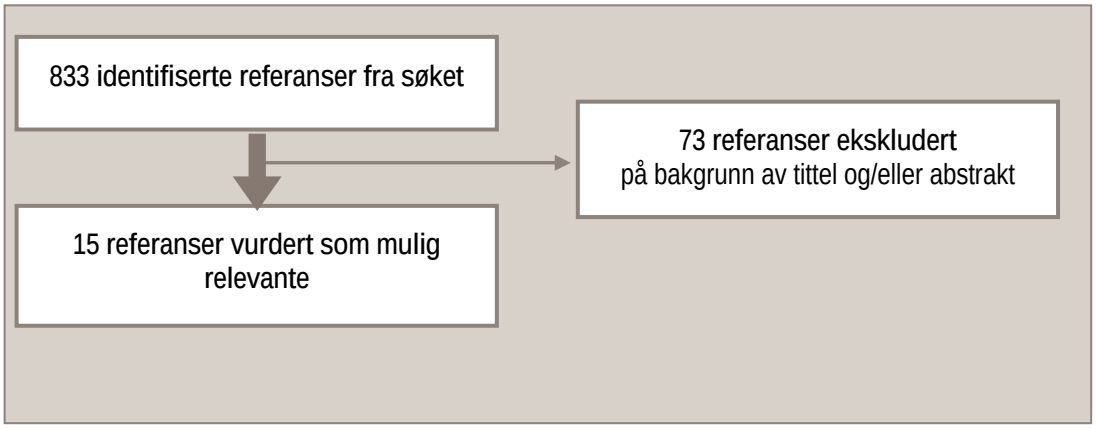


Figur 1. Flytskjema over identifisert litteratur.

Litteratursøk etter randomiserte kontrollerte studier

Litteratursøket etter randomiserte kontrollerte studier resulterte i 833 referanser. Vi vurderte 15 av de identifiserte referansene til å være mulig relevante i henhold til inklusjonskriteriene, figur 2.

Hovedårsakene til eksklusjon var at referansene ikke oppfylte inklusjonskriteriet for studiedesign (randomiserte kontrollerte studier) og at referansene omhandlet ulike tobakkavvenningstiltak og ikke snus som røykeavvenningstiltak.



Figur 2. Flytskjema over identifisert litteratur.

Liste over referanser

Nedenfor følger lister over mulig relevante systematiske oversikter og randomiserte kontrollerte studier.

Systematiske oversikter

Referansene er sortert alfabetisk etter førsteforfatter.

(1) Baillie AJ, Mattick RP, Hall W, Webster P. Meta-analytic review of the efficacy of smoking cessation interventions. *Drug and Alcohol Review* 1994; 13(2):157-170.
Ref ID: 1158
Abstract: Analyzed evaluations of the efficacy of smoking cessations and compared 146 estimates of the difference in abstinence rates between treated and control conditions from 85 publications. Simple advice to quit and brief intervention techniques, such as nicotine chewing gum and behavioral techniques, were all found to be significantly better than relevant control conditions in promoting abstinence. In 5 studies of acupuncture compared with controls, results consistently found no benefit for acupuncture. (PsycINFO Database Record (c) 2012 APA, all rights reserved)

(2) Lee PN. Summary of the epidemiological evidence relating snus to health. *Regul Toxicol Pharmacol* 2011; 59(2):197-214.
Ref ID: 536
Abstract: Interest in snus (Swedish-type moist snuff) as a smoking alternative has increased. This wide-ranging review summarizes evidence relating snus to health and to initiation and cessation of smoking. Meta-analyses are included. After smoking adjustment, snus is unassociated with cancer of the oropharynx (meta-analysis RR 0.97, 95% CI 0.68-1.37), oesophagus (1.10, 0.92-1.33), stomach (0.98, 0.82-1.17), pancreas (1.20, 0.66-2.20), lung (0.71, 0.66-0.76) or other sites, or with heart disease (1.01, 0.91-1.12) or stroke (1.05, 0.95-1.15). No clear associations are evident in never smokers, any possible risk from snus being much less than from smoking. "Snuff-dipper's lesion" does not predict oral cancer. Snus users have increased weight, but diabetes and chronic hypertension seem unaffected. Notwithstanding unconfirmed reports of associations with reduced birthweight, and some other conditions, the evidence provides scant support for any major adverse health effect of snus. Although some claims that snus reduces initiation or encourages quitting are unsoundly based, snus seems not to increase initiation, as indicated by few smokers using snus before starting and current snus use being unassociated with smoking in adults (the association in children probably being due to uncontrolled confounding), and there are no reports that snus discourages quitting. 2010 Elsevier Inc

(3) Tomar SL, Fox BJ, Severson HH. Is Smokeless Tobacco Use an Appropriate Public Health Strategy for Reducing Societal Harm from Cigarette Smoking? *International journal of environmental research and public health* 2009; 6(1):10-24.
Ref ID: 1276
Abstract: Four arguments have been used to support smokeless tobacco (ST) for harm reduction: (1) Switching from cigarettes to ST would reduce health risks; (2) ST is effective for smoking cessation; (3) ST is an effective nicotine maintenance product; and (4) ST is not a "gateway" for cigarette smoking. There is little evidence to support the first three arguments and most evidence suggests that ST is a gateway for cigarette smoking. There are ethical challenges to promoting ST use. Based on the precautionary principle, the burden of proof is on proponents to provide evidence to support their position; such evidence is lacking

Randomiserte kontrollerte studier

Referansene er sortert alfabetisk etter førsteforfatter.

(1) Drug and Non-Drug Treatment Strategies to Assist Smoking Cessation. *Therapie* 2003; 58(6):479-497.
Ref ID: 804

(2) Barrett SP, Wagner E. A comparison between quick-release nicotine lozenges and Swedish-style snus for the acute management of craving. *Tob Control* 2011; 20(5):386.
Ref ID: 1

(3) Barrett SP, Campbell ML, Temporale K, Good KBP. The acute effect of Swedish-style snus on cigarette craving and self-administration in male and female smokers. *Human psychopharmacology* 2011; 26(1):58-62.
Ref ID: 589
Abstract: Introduction: Swedish-style snus (SS) has recently garnered controversy for its proposed use as a smoking cessation aid and/or harm reduction tool. However, to date, little work has been done to evaluate the extent to which SS affects cigarette cravings and smoking behavior under double-blind controlled conditions. Methods: During four double-blind placebo-controlled randomized sessions, 15 smokers (8 male) administered SS, placebo (nicotine/tobacco-free) snus (PS), a nicotine-containing lozenge (NL), or a placebo lozenge (PL) for 30 min and assessed their effects using Visual Analogue Scales and the Brief Questionnaire of Smoking Urges. They could then self-administer their usual brand of cigarettes using a progressive ratio task over the next 60 min. Following the completion of their final session, 11 participants (6 male) ranked each of the products used in the study in terms of their preferences. Results: Relative to the other products, SS was associated with a decreased intention to smoke as well as a delayed onset of cigarette smoking in men but not women. However, SS administration was also associated with increased feelings of frustration and irritability relative to NL and SS was ranked as being the least preferred product used in the study. Discussion: Findings suggest that SS is effective in acutely suppressing craving and smoking in at least some smokers, but that its acceptability may be limited. Copyright 2011 John Wiley & Sons, Ltd

(4) Burton D, Chakravorty B, Weeks K, Flay BR, Dent C, Stacy A et al. Outcome of a tobacco use cessation randomized trial with high-school students. *Subst Use Misuse* 2009; 44(7):965-980.
Ref ID: 652
Abstract: This study analyzed quantitative data on tobacco use and dependency for 3,589 high-school students, qualitative data for 448 students, and outcome data for a randomized trial comparing the efficacy of two cessation interventions and a control condition for 337 students. Data were collected from 1988 through 1992 in California and Illinois as part of a larger longitudinal study. Smokeless tobacco users, but not smokers, were more likely than controls to maintain cessation for 4 months:

biochemically validated cessation at 4 months was 6.5 versus 3.2 for smokers and 14.3 versus 0.0 for smokeless tobacco users. Implications and limitations are discussed. 2009 Informa UK Ltd All rights reserved

(5) Caldwell B, Burgess C, Crane J. Randomized crossover trial of the acceptability of snus, nicotine gum, and Zonnic therapy for smoking reduction in heavy smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2010; 12(2):179-183.
Ref ID: 44
Abstract: INTRODUCTION: Novel approaches to nicotine replacement therapy (NRT) are needed to improve the modest long-term quit rate of 10%. Snus (Swedish tobacco) and Zonnic (oral nicotine sachet) rapidly deliver nicotine via buccal absorption and have potential as NRTs. As a prelude to formal evaluation of either product as a smoking cessation therapy, it is necessary to determine their acceptability and the willingness of smokers to use them in populations with no history of access to oral tobacco products.METHODS: An open-label crossover study of ad libitum snus, Zonnic, and nicotine gum among 63 smokers for 2 weeks each, and smoking reduction if the subjects did not feel the desire to smoke. Diary cards recorded use of products and cigarettes; formal and ad hoc scales measured urges to smoke, withdrawal symptoms, and the sensory quality of the products.RESULTS: Subjects preferred snus and Zonnic over gum. Snus and Zonnic were superior to gum in reducing urges to smoke and caused fewer side effects. All three products suppressed withdrawal symptoms. Subjects reduced their smoking by Ms of 33%, 37%, and 42% during the gum, snus, and Zonnic fortnights, respectively.DISCUSSION: Most subjects reported a strong desire to use Zonnic or snus to quit smoking. Subjects preferred snus and Zonnic, which both had significantly fewer gastrointestinal side effects than gum and resulted in greater reductions in smoking. Snus and Zonnic are effective in suppressing desires to smoke and reducing smoking, and further studies are warranted to investigate their effect on long-term quit rates

(6) Carpenter MJ, Gray KM. A pilot randomized study of smokeless tobacco use among smokers not interested in quitting: Changes in smoking behavior and readiness to quit. *Nicotine and Tobacco Research* 2010; 12(2):136-143.
Ref ID: 629
Abstract: Introduction: Several prior studies suggest that smokeless tobacco use results in less carcinogenic risk than does cigarette smoking. Whether smokers will use smokeless tobacco is unclear, as is the impact of such use on long-term smoking behavior and cessation. It is equally plausible that smokeless tobacco use among smokers could either (a) increase total tobacco exposure and undermine motivation to quit or (b) decrease overall tobacco exposure, motivate smokers to quit, and enhance cessation. Either outcome is of major public health significance. Methods: In this small (N = 31), short-term (2 week) pilot study, smokers uninterested in quitting were randomized to (a) receive Ariva or Stonewall (both spitless and smokeless tobacco lozenges) or (b) continue smoking conventional cigarettes. Results: Ariva/Stonewall use led to a significant reduction (40%, 95% CI: 24%-55%) in cigarettes per day, no significant increases in total tobacco use (cigarettes + Ariva/Stonewall; $p > .05$), and significant increases in two measures of readiness to quit, either in the next month ($p < .001$) or within the next 6 months ($p = .04$), as well as significant increases in self-efficacy to quit smoking ($p < .001$). No such changes were found among smokers maintained on conventional cigarettes. Discussion: These results suggest no deleterious effect on short-term smoking and quitting behavior among smokers who use smokeless tobacco. More broadly, this study suggests a strong need for a large prospective randomized clinical trial to more accurately assess the long-term viability of smokeless tobacco use as a method for cessation induction among unmotivated smokers. The Author 2010. Published by Oxford University Press on behalf of the Society for Research on Nicotine and Tobacco

(7) Edwards BQ. Studies in tobacco harm reduction: The role of context in subjective effects and behavioral responses to a reduced exposure tobacco product. *Dissertation Abstracts International: Section B: The Sciences and Engineering* 2008; 69(1-B):255.
Ref ID: 1117
Abstract: Cigarette smoking remains one of the most important and preventable

causes of morbidity and mortality. Tobacco harm reduction has been recognized as one component of a comprehensive tobacco control effort. Potential reduced exposure tobacco products (PREPs), particularly low-nitrosamine smokeless tobacco products, have attracted attention as promising harm reduction products. However, there is little research to date to support a viable role for these products within tobacco harm reduction efforts. The current study included two trials of smokers' evaluations and use of a low nitrosamine smokeless tobacco product. Both trials employed a between-subjects design and all participants were screened to ensure eligibility. In the first trial, participants were randomly assigned to evaluate information emphasizing harm reduction (n=20) or convenience factors (n=20) and to evaluate the tobacco product. In the second trial, all participants evaluated the product during 3 lab sessions. Participants were randomly assigned to an experimental (n=21) or control (n=19) condition at the end of the 1st session. Participants in the experimental group tried the tobacco product daily for 5 days until the 2nd lab session; those in the control group had no additional use of the tobacco until the 2nd lab session. Between lab sessions 2 and 3, all participants were free to use the tobacco product if they chose, but use was not required. Participants recorded all their tobacco use between lab sessions. Findings from trial one revealed no statistically significant differences in evaluations of information emphasizing harm reduction potential versus convenience factors of a non-smoked tobacco. Further, results from the 2nd trial demonstrated a statistically significant improvement in overall evaluations of the product by itself and compared to cigarettes regardless of experimental condition. However, participants in the control condition demonstrated a small but significant decrease in smoking when they were free to use the trial tobacco outside the lab. The majority of participants stated they would try the tobacco product again, primarily when smoking was not permitted and to cut down on smoking. The contribution of this dissertation research is presented, followed by a discussion of the findings and suggestions for future research. (PsycINFO Database Record (c) 2012 APA, all rights reserved)

(8) Fagerstrom K, Rutqvist LE, Hughes JR. Snus as a smoking cessation Aid: A randomized placebo-controlled trial. *Nicotine and Tobacco Research* 2012; 14(3):306-312.
Ref ID: 570
Abstract: Introduction: Snus is a low-nitrosamine smokeless product that appears to be safer than other smokeless products. Evidence indicates that snus has been used as an effective smoking cessation aid in Scandinavia. No randomized controlled trial has directly tested the efficacy of snus for smoking cessation. Methods: This randomized, double-blind, placebo-controlled multicentre trial tested the efficacy of snus for smoking cessation. Of the 250 subjects, 125 were randomized to active or placebo snus sachets. Subjects were followed up through 28 weeks after randomization. In total, 5 clinical visits and 8 telephone contacts were scheduled. Primary outcome measure was biologically verified continuous smoking abstinence from Week 6 through 28. Results: The continuous abstinence rate during Weeks 6-28 in the snus and placebo groups was 4.0% and 1.6% (odds ratio [OR]: 2.5, 95% CI: 0.4-27), respectively. The point prevalence abstinence rate at 6 weeks was 18.4% in the snus group versus 8.8% in the placebo group (OR: 2.3, 95% CI: 1.1-5.0, p = .03). At Week 28, the difference in favor of the snus group was not statistically significant (12.8% vs. 7.2%, OR: 1.9, 95% CI: 0.8-4.4). Snus was generally well tolerated. Treatment-related adverse events that were more common in the snus group were generally mild and included nausea, dyspepsia, gingivitis, hiccups, and dizziness. Conclusions: Although the cessation rates generally were low and, at 28 weeks, did not differ between active and placebo, early quit rates suggested that snus was superior and with similar effect sizes to those with nicotine replacement. These results suggest that snus needs to be further researched as a smoking cessation treatment. The Author 2011. Published by Oxford University Press on behalf of the Society for Research on Nicotine and Tobacco. All rights reserved

(9) Hatsukami DK, Jensen J, Anderson A, Broadbent B, Allen S, Zhang Y et al. Oral tobacco products: Preference and effects among smokers. *Drug & Alcohol Dependence* 2011; 118(2-3):230-236.
Ref ID: 1238
Abstract: BACKGROUND: Recently, oral tobacco products have been marketed specifically towards cigarette smokers. These products come in different nicotine doses

and formulations (snus vs. lozenge). To date, little research has been conducted to determine how smokers respond to these products. The goal of this study was to examine if smokers prefer certain oral tobacco products based on their specific characteristics. METHODS: Smokers interested in quitting underwent a sampling phase and a treatment phase. The sampling phase consisted of testing five different products varying in nicotine dose (high vs. moderate vs. low) and formulation (snus vs. lozenge): General Snus, Camel Snus, Marlboro Snus, Stonewall and Ariva. Each product was sampled in the natural environment on separate days. At the end of the sampling period, subjects chose which product they would use during the 2-week cigarette abstinence phase. RESULTS: General Snus (high nicotine) was not preferred by any smoker. No significant differences in preferences were observed across the other tobacco products. During the smoking cessation phase, Camel Snus was generally associated with greater craving relief and satisfaction, reduced use of cigarettes, and greater abstinence during follow-up compared to other products. CONCLUSION: There were no differences in preferences for four of the five oral tobacco products but higher nicotine oral tobacco products were associated with better cessation outcomes among smokers who chose these products

(10) Joksic G, Spasojevic-Tisma V, Antic R, Nilsson R, Rutqvist LE. Randomized, placebo-controlled, double-blind trial of Swedish snus for smoking reduction and cessation. *Harm Reduction Journal* 2011; 8(1):25.
Ref ID: 1014
Abstract: UNLABELLED: ABSTRACT: BACKGROUND: Epidemiological studies suggest that smokeless tobacco in the form of Swedish snus has been used by many smokers in Scandinavia to quit smoking, but the efficacy of snus has so far not been evaluated in controlled clinical trials. METHODS: We conducted a randomized, double-blind, placebo-controlled, clinical trial aimed at assessing the efficacy of snus to help adult cigarette smokers in Serbia to substantially reduce, and, eventually, completely stop smoking. The study enrolled 319 healthy smokers aged 20-65 years at two occupational health centers in Belgrade, Serbia. Most of them (81%) expressed an interest to quit rather than just reduce their smoking. Study products were used ad libitum throughout the 48-week study period. The main study objective during the first 24 weeks was smoking reduction. The primary end-point was defined as a biologically verified reduction of >= 50% in the average number of smoked cigarettes per day during week 21-24 compared to baseline. During week 25-48 participants were actively instructed to stop smoking completely. Outcome measures of biologically verified, complete smoking cessation included 1-week point prevalence rates at clinical visits after 12, 24, 36, and 48 weeks, as well as 4-, 12- and 24-week continued cessation rates at the week 36 and 48 visits. RESULTS: At the week 24 visit, the proportion of participants who achieved the protocol definition of a >= 50% smoking reduction was similar in the two treatment groups. However, the proportion that reported more extreme reductions (>= 75%) was statistically significantly higher in the snus group than in the placebo group ($p < 0.01$). The results for biologically verified complete cessation suggested that participants in the snus group were more likely to quit smoking completely than the controls; the odds ratio (snus versus placebo) for the protocol estimates of cessation varied between 1.9 to 3.4, but these ratios were of borderline significance with p-values ranging from 0.04-0.10. Snus was well tolerated and only 2/158 (1.3%) participants in the snus group discontinued treatment due to an adverse event (in both cases unrelated to snus). CONCLUSIONS: Swedish snus could promote smoking cessation among smokers in Serbia, that is, in a cultural setting without traditional use of oral, smokeless tobacco. TRIAL REGISTRATION: www.clinicaltrials.gov, identifier: NCT00601042

(11) Kotlyar M, Hertsgaard LA, Lindgren BR, Jensen JA, Carmella SG, Stepanov I et al. Effect of oral snus and medicinal nicotine in smokers on toxicant exposure and withdrawal symptoms: a feasibility study. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2011; 20(1):91-100.
Ref ID: 7
Abstract: BACKGROUND: Smokeless, spitless tobacco products are being introduced and marketed as cigarette substitutes. Data are needed regarding how smokers interested in cessation would use these products, the levels of resultant toxicant exposure, and the feasibility of using these products as aids for tobacco cessation.METHODS: Smokers were randomized to receive Camel Snus (n = 51), Taboka

(n = 52), or medicinal nicotine (n = 27) and required to quit smoking for 4 weeks. Measures of toxicant exposure and symptoms of craving and withdrawal were assessed prior to and during product use.RESULTS: Concentrations of exhaled carbon monoxide, urinary cotinine, urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), and urinary N'-nitrosonornicotine and its glucuronide (total NNN) were significantly (P values <0.05) lower at the end of treatment in each group except for total NNN in those receiving Camel Snus (P = 0.066). A significant group × time effect was observed for total NNAL concentrations (P = 0.002) with the decrease greatest in the medicinal nicotine group and smallest decrease in the Camel Snus group. No significant differences between groups were found in craving and withdrawal symptoms.CONCLUSIONS: Enrolling smokers into a cessation study utilizing newer smokeless tobacco products is feasible. Camel Snus and Taboka use was not found to be superior to medicinal nicotine in reducing withdrawal symptoms but decreases in NNAL were smaller in users of Camel Snus.IMPACT: This study demonstrates the feasibility of conducting a smoking cessation study utilizing these newer tobacco products. An appropriately powered study is needed to assess smoking cessation rates using these newer products compared with established, safer products such as medicinal nicotine

(12) Lunell E, Curvall M. Nicotine delivery and subjective effects of Swedish portion snus compared with 4 mg nicotine polacrilex chewing gum. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2011; 13(7):573-578.
Ref ID: 17
Abstract: INTRODUCTION: Snus availability has been claimed to have contributed to the low rates of smoking among Swedish men and made possible the transfer to a less harmful form of nicotine dependence.METHODS: Fourteen cigarette smokers were randomly assigned to 2 types of 1 g Swedish portion snus and 4 mg nicotine polacrilex (NP) chewing gum in open-label, single-dose crossover study. Nicotine delivery and pharmacokinetics were estimated, and self-reports of subjective effects were obtained using Visual Analogue Scales (VASs).RESULTS: Extracted dose from the NP gum averaged 2.56 mg compared with 2.12 and 2.18 mg, respectively, for Swedish portion snus. This resulted in a slightly larger area under the curve (AUC) for the NP chewing gum. The rise of the nicotine plasma concentration was faster for Swedish snus. Median T(max) was shorter, 30 min for snus compared with 45 min for the NP gum. The lower C(max) of NP gum compared with the snus products in spite of larger AUC may be explained by slower absorption from the chewing gum. The faster absorption of nicotine from Swedish portion snus was mirrored in a higher VAS score for "head rush." Craving/urges to smoke decreased similarly for all treatments. Salivation and throat burn were rated higher for the 4 mg NP gum compared with both types of snus.CONCLUSIONS: Swedish snus produced higher maximum blood nicotine concentration in shorter time and with a quicker onset of "head rush" compared with 4 mg NP chewing gum in spite of a smaller extracted dose. The quicker onset of "head rush" and supposedly higher satisfaction from snus may partly explain the widespread use of snus for stopping smoking in Sweden

(13) Mendoza-Baumgart MI, Tulunay OE, Hecht SS, Zhang Y, Murphy S, Le C et al. Pilot study on lower nitrosamine smokeless tobacco products compared with medicinal nicotine. *Nicotine and Tobacco Research* 2007; 9(12):1309-1323.
Ref ID: 717
Abstract: Smokeless tobacco (ST) products have the potential to be used as a harm reduction method for cigarette smokers. These products can deliver significantly less toxicants than cigarettes, although they are not toxicant free nor harmless. It is important to examine potential health risks and benefits of these products. These two small pilot studies examined the effects of two different ST products (Exalt and Ariva) compared with medicinal nicotine, another potential harm reduction product. Dependent, healthy adult cigarette smokers, who were motivated to quit smoking, underwent 1 week of baseline smoking measurement. They were then asked to quit smoking and were randomly assigned to use either an ST product or a medicinal nicotine lozenge (MNL, Commit) for 2 weeks, then crossed over to use the other product for 2 weeks. In the last week, following the sampling phase, subjects could choose the product they wished to use. Assessments were made repeatedly during baseline cigarette use and throughout the 5 weeks of treatment. Outcome measures included biomarkers for tobacco exposure and subjective, physiological, and behavioral res-

ponses. Tobacco-specific carcinogen uptake was greater from Exalt than from the MNL, and was comparable between the MNL and Ariva. Physiological effects and subjective effects on withdrawal and craving were comparable among Exalt, Ariva, and the MNL. Ariva was preferred over the MNL, which was preferred over Exalt. With the exception of medicinal nicotine products, low-nitrosamine ST products have the greatest potential to result in reduced toxicant exposure compared with other combustible reduced exposure products and have promise for reducing individual risk for disease. However, the population effect of marketing of such products as reduced exposure/ reduced risk is unknown. The need for further research in this area and regulation of tobacco products is evident

(14) Sarkar M, Liu J, Koval T, Wang J, Feng S, Serafin R et al. Evaluation of biomarkers of exposure in adult cigarette smokers using Marlboro snus. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2010; 12(2):105-116.
Ref ID: 33
Abstract: INTRODUCTION: It has been reported that adult smokers (AS) may be considering smokeless tobacco products as an alternative to smoking. The objective of this study was to evaluate the change in exposure in AS using Marlboro snus (MSNUS) (a tobacco pouch product in test market in June 2007).METHODS: AS were randomized into the following groups--CS: subjects (n = 30) continue smoking their own brand; DU: subjects (n = 60) reduced their daily cigarette consumption by >or=50% and were allowed to use MSNUS; SN: subjects (n = 15) stopped smoking their cigarettes but were allowed to use MSNUS; NT: subjects (n = 15) were not allowed to use any tobacco products for the entire duration of the 8-day study. Biomarkers of smoke exposure (BOE) measured at baseline and postbaseline were 24-hr urinary excretion of metabolites of N-nitrosamines, nicotine (urine and plasma), aromatic amines, benzene, and polycyclic aromatic hydrocarbon; urine mutagenicity; and carboxyhemoglobin at various timepoints.RESULTS: Statistically significant ($p < .05$) reductions in all the urinary BOE were observed in the DU group compared with the CS group. After correcting for the residual effect, a proportionate reduction (approximately 50%) in most of the biomarkers was observed. Even larger reductions, similar to the NT group, were observed in the SN group.DISCUSSION: The proportionate reduction in exposure when reducing the number of cigarettes by 50% and using MSNUS, under the consumption patterns observed, suggest that the AS did not appear to alter their smoking behavior. The added exposure from MSNUS usage in this group was minimal. The AS sustained substantial reductions in exposure when using MSNUS exclusively

(15) Tonnesen P, Mikkelsen K, Bremann L. Smoking cessation with smokeless tobacco andgroup therapy: An open, randomized, controlled trial. *Nicotine and Tobacco Research* 2008; 10(8):1365-1372.
Ref ID: 678
Abstract: Smokeless tobacco might be effective as an adjunct for smoking cessation. We evaluated the efficacy of smokeless tobacco and group support for smoking cessation in an open, randomized study that compared smokeless tobacco plus group support versus group support only. The study enrolled 263 healthy smokers (M age = 49 years) who smoked a mean of 24 cigarettes/day, with a mean of 31 pack-years. Smokeless tobacco was provided for 7 weeks (or up to 12), combined with eight group support visits provided by nurses. The control group received group support only. Smoking cessation rates were statistically significantly better in the smokeless tobacco group than in the control group during the first 7 weeks. Point-prevalence abstinence rates at 7 weeks were 36.4% versus 20.8% (OR=2.52, p=.001), respectively; and continuous abstinence rates from weeks 4 to 7 were 31.5% versus 19.2% (OR=1.94, p=.023), respectively. The primary outcomes (i.e., 6-month point prevalence) were 23.1% versus 20.8%, respectively (OR=1.31, ns). Smokeless tobacco was relatively well tolerated, although 15 subjects (11.2%) stopped use due to adverse events. A total of 25 subjects (17.5%) were still using smokeless tobacco after 6 months. This trial demonstrated short-term efficacy of smokeless tobacco in combination with group support for smoking cessation but no long-term efficacy

Vedlegg

Søkestrategier

Systematisk litteratursøk

Prosjekt: **Snusavvenning**
Databaser: Ovid: Embase, Medline, PsycINFO. Cochrane Library: CDSR (Cochrane Database of Systematic Reviews), CENTRAL (Cochrane Central Register of Controlled Trials), Technology Assessments Database. Centre for Reviews and Dissemination (CRD): DARE (Database of Abstracts of Reviews of Effects). Web of Science (i Web of Knowledge), SveMed+, PubMed
Dato: 21.6.2012
Resultat: 76 Systematiske oversikter (SR, HTA)
833 Randomiserte kontrollerte studier (RCT)/kontrollerte studier
909 totalt (1298 inkl. duplikater)
Utført av: Ingrid Harboe, forskningsbibliotekar

Tegnforklaring:

/	Kode for MeSH (emneord); f.eks. Smokeless tobacco/
.tw	Text word (tekstord); søk etter tekstord i tittel, abstract, keyword
:ti,ab,kw	Søk etter tekstord i tittel, abstract, keyword (Cochrane Library)
*	Trunkering; søk etter flertall/ annen endelse av søkeordet

Database: Embase 1980 to 2012 Week 24
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, PsycINFO 1987 to June Week 2 2012 (kombinert søk)
Dato: 20.06.2012
Resultat: 58 Systematiske oversikter (SR)
617 Randomiserte kontrollerte studier (RCT)
Studiefilter SR: ”reviews (maximizes specificity)”; spesifikt
RCT: "therapy (best balance of sensitivity and specificity)", medium spesifikt

Searches		Results
1	smokeless tobacco/	5499
2	Tobacco, Smokeless/ use prmz [kode: Medline]	2539
3	(chewing tobacco* or oral tobacco* or spit tobacco* or smokeless tobacco* or snuff* or snus* or quid* or chew* or plug*).tw.	56101
4	or/1-3	57384

5	"Tobacco Use Cessation"/ use prmz	579
6	("abstain* from" or "break* off" or cessation* or cease or ceasing or "cut* out" or discontinu* or end or ending or finish or "give up" or halt or halting or pause or quit* or respite or stop* or suspend* or terminat*).tw.	1929779
7	tobacco dependence/dt, th use emez [Drug Therapy, Therapy]	3592
8	tobacco dependence/pc, rh use emez [Prevention, Rehabilitation]	1313
9	"Tobacco Use Cessation Products"/ use prmz	271
10	smoking cessation/	56319
11	or/5-10	1950035
12	4 and 11	6385
13	limit 12 to "reviews (maximizes specificity)"	84
14	12 and systematic* review*.tw.	36
15	13 or 14	89
16	remove duplicates from 15	58
17	limit 12 to "therapy (best balance of sensitivity and specificity)"	962
18	remove duplicates from 17	617
19	18 use emez [kode: Embase]	453
20	18 use prmz	67
21	18 not (19 or 20)	97
22	16 use emez	33
23	16 use prmz	15
24	22 or 23	48
25	16 not 24	10

Database: Cochrane Library
Dato: 20.06.2012
Results: 16 Systematiske oversikter (CDSR)
516 Kontrollerte studier (CENTRAL)

Søk:

#1	MeSH descriptor Tobacco, Smokeless, this term only	97
#2	(chewing tobacco* or oral tobacco* or spit tobacco* or smokeless tobacco* or snuff* or snus* or quid* or chew* or plug*):ti,ab,kw	1950
#3	(#1 OR #2)	1950
#4	MeSH descriptor Tobacco Use Cessation explode all trees	2572
#5	("abstain* from" or "break* off" or cessation* or cease or ceasing or "cut* out" or discontinu* or end or ending or finish or "give up" or halt or halting or pause or quit* or respite or stop or suspend or terminat*):ti,ab,kw	74785
#6	MeSH descriptor Tobacco Use Cessation Products explode all trees	65
#7	(#4 OR #5 OR #6)	74785
#8	(#3 AND #7)	541

Database: **CRD DARE** (Database of Abstracts of Reviews of Effects)
Dato: 20.06.2012
Result: 27 Systematiske oversikter
Søk:

1	MeSH DESCRIPTOR Tobacco, Smokeless	5
2	("chewing tobacco*" or "oral tobacco*" or "spit tobacco*" or "smokeless tobacco*" or snuff* or snus* or quid* or chew* or plug*).)	138
3	(("abstain* from" or "break* off" or cessation* or cease or ceasing or "cut* out" or discontinu* or end or ending or finish or "give up" or halt or halting or pause or quit* or respite or stop* or suspend* or terminat*).)	7316
4	MeSH DESCRIPTOR Tobacco Use Cessation EXPLODE ALL TREES	324
5	#1 OR #2	139
6	#3 OR #4	7316
7	#5 AND #6	36
8	(#7) IN DARE, HTA	27

Database: **Web of Science**
Dato: 21.06.2012
Resultat: 35 (Systematiske) oversikter
Søk: Topic=(smokeless tobacco) AND Topic=(cessation) AND Document Types=(Review) Timespan=All Years. Databases=SCI-EXPANDED, SSCI

Datebase: **SveMed+**
Dato: 21.6.2012
Resultat: 4 Oversikter
11 Enkeltstudier

Sök:		Antal träffar
1	smokeless tobacco OR snus OR exp:"Tobacco, Smokeless"	140
2	cessation OR tobacco cessation OR exp:"Smoking Cessation" Limits: doctype:"översikt"	40
3	#1AND #2 oversikter	4
4	#1 AND #2 artikler	11

Database: **PubMed**
Dato: 21.06.2012
Resultat: 1 unik systematisk oversikt
Søk: Smokeless tobacco cessation and Systematic Review / Clinical study
Limit: 2012