Gradual versus abrupt smoking cessation: a randomised controlled non-inferiority trial

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Abstract

Background

Most smoking cessation guidelines advise quitting abruptly. However, many quit attempts involve gradual cessation. If gradual is as successful, smokers can be advised to quit either way.

Objectives

To examine the success of quitting smoking by reducing first relative to quitting abruptly.

Design

Randomised controlled non-inferiority trial.

Setting

Primary care clinics in England.

Participants

697 adult smokers addicted to tobacco.

Interventions

Participants quit abruptly or reduced smoking by 75% in the two weeks before quitting. Both arms received behavioural support from nurses and used nicotine replacement before and after quit day.

Outcome measures

The primary outcome measure was prolonged validated smoking abstinence 4 weeks after quit day. The secondary outcome was prolonged validated 6-month abstinence.

Results

At 4 weeks, 39.2% (95%CI: 34.0, 44.4) of the participants in the gradual arm were abstinent compared with 49.0% (95%CI: 43.8, 54.2) in the abrupt arm (relative risk (RR) 0.80; 95%CI, 0.66, 0.93). At six months, 15.5% (95% CI: 12.0, 19.7) of the participants in the gradual arm were abstinent compared with 22.0% (95% CI: 18.0, 26.6) in the abrupt arm (RR 0.71; 95%CI, 0.46, 0.91). At four weeks, 34.6% of participants who preferred to quit gradually and were allocated to quit that way were abstinent compared with 42.0% who were allocated to quit abruptly, against their preference.

Limitations

Blinding was impossible. Most participants were white.

Conclusions

Quitting smoking abruptly is more likely to lead to lasting abstinence than cutting down first, even for smokers who initially prefer to quit by reduction.

Trial Registration

Registered on the International Standard Randomised Controlled Trial Number Register before the start of participant enrolment (ISRCTN22526020). Online at: http://controlled-trials.com/ISRCTN22526020.

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Introduction

Conventionally smokers are advised to quit abruptly by setting a quit day and stopping smoking in one step. Worldwide, guidelines for smoking cessation generally recommend stopping smoking abruptly and do not support reducing cigarettes smoked first (2-4); however, many smokers report stopping gradually (5-7). It is important to know whether smokers should be advised against gradual cessation because it might produce lower success rates.

Evidence on whether gradual cessation is less effective than abrupt cessation is conflicting. Observational data on quit attempts made mainly without behavioural support suggest that stopping abruptly is superior (5, 8). However, a Cochrane review of ten randomised trials suggests there may be little difference in quit rates achieved using the two approaches (9), with a relative risk (RR) of 0.94 (95% confidence intervals (CI): 0.79 to 1.13). Several trials included in the review had design features that make it uncertain that differences in quit rates were solely due to the method used to achieve abstinence. None were designed to assess non-inferiority, and the pooled 95%CI obtained encompasses a substantial reduction in the efficacy of quitting gradually compared with quitting abruptly. We conducted a large trial to test whether an initial gradual reduction in smoking produces non-inferior quit rates to abrupt cessation.

Methods

Design

We randomized adult smokers to either gradually reduce their tobacco use over two weeks prior to a planned quit day, or to stop smoking abruptly on a planned quit day. The gradual cessation group received short acting nicotine replacement therapy (NRT) and nicotine

patches prior to the quit day. The abrupt cessation group received only nicotine patches prior to the quit day. Both groups received behavioural counseling, as well as nicotine patches and short acting NRT following the quit day. Our primary outcome was validated abstinence at 4 weeks following the quit day. We also evaluated 6 month abstinence and whether outcomes differed according to participants' preferred method of quitting.

Participants

We recruited adult smokers addicted to tobacco, defined as those smoking at least 15 cigarettes/12.5 grams of loose tobacco daily and/or having end-expiratory carbon monoxide (CO) concentration of at least 15 parts per million (ppm). Participants had to be willing to quit smoking two weeks after trial enrolment. Exclusion criteria were: currently undergoing cessation treatment; cautions for the use of NRT; participation in other medicinal trials; circumstances that would mean the demands of trial participation would not be met. People with dependence upon alcohol or illicit drugs and severe acute or chronic medical or psychiatric conditions were included unless their conditions were so incapacitating that meeting the demands of the trial was very unlikely.

The lead general practitioner at 31 volunteer practices in England searched their electronic patient records and wrote to all registered patients who smoked to invite them into the study. Potential participants were encouraged to telephone the researchers, who explained the trial and screened patients for eligibility. Eligible smokers were booked for an appointment with a research nurse, where the study was explained, eligibility confirmed, and written informed consent obtained.

Interventions

Participants were asked to set a quit day two weeks after enrolment and the intervention differed between arms only during these two pre-quit weeks. In the gradual quit arm, participants aimed to reduce smoking to half of baseline by the end of the first week (visit -1), and to a quarter of baseline at the end of the second week (visit 0), in daily increments. Reduction over two weeks was chosen because there is qualitative evidence that this keeps people more focused on quitting than longer reduction (10); a trial (11) suggests that it is more effective than longer reduction; and because the two week preparation for quit day is current practice (12). Participants in the gradual reduction arm chose one of three structured reduction programmes: scheduled, hierarchical, or smoke-free periods reduction. In scheduled reduction, participants used a timer (usually a mobile phone) to schedule inter-cigarette intervals and smoked only when the timer sounded or for five minutes thereafter. The time between cigarettes lengthened daily (1, 2). In hierarchical reduction, participants rated cigarettes from most to least favourite and progressively eliminated either their favourite or least favoured cigarettes. In smoke-free periods, participants mapped their regular day and noted the 30 minute periods within which they smoked. They then progressively eliminated half, and then three quarters of these.

In all cases, the nurse drew up reduction schedules with the participant to boost understanding and memory, and discussed strategies to prompt adherence to the schedules. Smoking reduction is more successful when participants use NRT (13) so we provided 21mg/24 hour nicotine patches and a choice of short-acting NRT products (gum, lozenge, nasal spray, sub-lingual tablet, inhalator, mouth spray) during the reduction period. For products such as gum and lozenge the instruction was to use one dose per cigarette missed. The short-acting NRT in the gradual arm was used to try to equalise blood nicotine concentrations in each trial arm prior to quitting.

Between baseline appointment and quit date, participants in the abrupt cessation arm were asked to smoke as normal and not reduce. To balance the behavioural support time, participants identified the cigarettes they would find hardest to give up and planned strategies to avoid relapse after quit day. Prior to quitting, participants in the abrupt arm were asked to use 21mg/24 hour nicotine patches but no short-acting NRT. NRT was used in this arm prior to quit day because there is some evidence that pre-cessation NRT increases quit rates and this balanced this effect between arms (14).

Other than these differences, the treatment programme in both arms was identical. Participants were seen by a research nurse at their primary care practice weekly for two weeks prior to their quit day (baseline visit, visit -1), the day before their quit day (visit 0), thereafter weekly for four weeks after quitting (visits +1, +2, +3 and +4), and finally eight weeks after quit day (visit +8). The behavioural support from visit 0 onwards was withdrawal oriented therapy, typical of a UK smoking cessation clinic (12,15), and the same in both trial arms. Withdrawal-oriented therapy focuses on the commitment to abstain completely and provides support early, when withdrawal symptoms are at their worst and relapse most likely. Pharmacotherapy was identical in both arms from quit day onwards, consisting of a 21mg/24 hour nicotine patch plus a short-acting form of NRT of the participant's choice. Participants were encouraged to use the short-acting form liberally, in anticipation of or in response to cravings.

Randomisation

Participants were randomised 1:1 to gradual or abrupt cessation at the baseline visit. An independent statistician used Stata to accomplish randomisation stratified by research nurse,

with randomly ordered blocks of 2, 4, and 6 to ensure balance. After consent, the research nurse opened sealed numbered envelopes in turn. Where participants quit in pairs (e.g. husband and wife), one was allocated randomly and the other allocated to the same arm.

Sample size

Our chosen non-inferiority margin was equivalent to a relative risk (RR) of 0.81 or a 19% reduction in effectiveness of quitting gradually compared with abruptly. This is an absolute difference in quit rates of 9.5% at four weeks assuming 50% quit in the abrupt arm (16). Using a one-sided alpha of 5%, 343 participants per arm were needed to have 80% power to detect this difference in the primary outcome.

Measures

Participant demographics, smoking history, nicotine dependence and preference for gradual or abrupt quitting were recorded at baseline. At each subsequent clinic session we assessed amount smoked, salivary cotinine, and measured exhaled carbon monoxide. Tobacco withdrawal symptoms were also measured using the Mood and Physical Symptoms Scale (MPSS), and are presented here as the mean score for urges and the mean score for withdrawal symptoms (17). We also assessed the occurrence of adverse events and participants rated the severity of possible symptoms of nicotine overdose during the two weeks using NRT and smoking. Nicotine overdose symptoms were provided as a checklist and participants were asked: 'Have you been troubled by any of the following problems in the past 24 hours?' They rated each symptom on a scale ranging from 'Not at all' to 'Extremely'. All participants were asked to complete daily diaries in the two weeks prior to quit day to measure adherence to medication and behavioural instructions. Trial arm preference was re-assessed at four week follow-up.

The primary outcome was Russell Standard four-week abstinence. The Russell Standard allows a two week grace period from quit day for slips and uses an intention to treat approach, assuming people lost to follow-up are smokers. Russell Standard abstinence is validated by an exhaled carbon monoxide concentration of <10ppm (18). Secondary outcomes were Russell Standard abstinence at eight week and six month follow-up; seven-day point prevalence abstinence at four week, eight week and six month follow-ups, validated by exhaled carbon monoxide of <10ppm; and urges to smoke and nicotine withdrawal symptoms at one and four weeks follow-up.

Data analysis

In the analysis of abstinence, we present relative risks due to the high incidence of abstinence (>10%). The primary non-inferiority analysis (abstinence at 4 weeks) was based on a one-sided alpha of 0.05 and therefore a 90% confidence interval was calculated. In accordance with CONSORT (18), we interpreted this confidence interval in relation to our pre-determined non-inferiority margin (RR=0.81). To assess superiority, which is also advised in non-inferiority trials (19), we calculated RRs with 95% confidence intervals. All relative risks (non-inferiority and superiority) were estimated using marginal standardization via logistic regression (20), adjusting for nurse. Confidence intervals were calculated via percentile bootstrapping. These analyses were carried out using the prLogisticBootMarg (prLogistic package) in R.

Where couples were recruited, we randomised one member and allocated the second non-randomly to the same arm. As a sensitivity analysis, we re-analysed excluding the second member of a couple (who was non-randomly assigned).

We calculated the proportion of participants attending each of the two post-baseline visits prior to quit day (visits -1 and 0) and compared these proportions by arm, using a $\chi 2$ test with Yates' correction for the difference between proportions. Medication use before quit day was assessed and reported as percentage using a patch daily, whether short-acting NRT was used and the number of units of short-acting NRT consumed daily. Both smoking reduction (cigarettes per day (cpd)) and CO) and medication use were taken from the daily diary and participants without these data were excluded from the analysis.

For each participant, mean urge score and withdrawal score were calculated (at baseline, week +1 and +4) using their responses to the two urge questions and seven withdrawal questions of the MPSS, respectively. We used a linear generalised estimating equation (xtgee command in STATA) to explore differences in mean urge and withdrawal symptom scores across these four weeks, adjusting for nurse and repeated measures. Participants missing scores at all three time-points were excluded from this analysis, but otherwise all participants were included in the model.

We assessed the impact on abstinence at four weeks of a participant preferring to quit gradually, compared with abruptly or no preference. Using logistic regression with the same marginal standardization as for other abstinence outcomes, we analysed the effect of allocation to gradual cessation on 4-week abstinence stratified by baseline preference: prefer gradual, prefer abrupt, no preference.

Approvals

The study and protocol were authorised by the Nottingham Research Ethics Committee 2 (08/H0408/213), the Medicines & Healthcare products Regulatory Agency, local National

Health Service (NHS) Research & Development offices, and registered before participant enrolment (ISRCTN22526020).

Role of funding source

Funding was provided by the British Heart Foundation (PG/08/047/25082). The funder was not involved in the analysis of the data or the interpretation of the findings, and had no role in writing the manuscript or submitting it for publication.

Results

Recruitment

Of 1097 people enquiring, 697 were randomised (355 to the abrupt arm and 342 to the gradual arm) by 23 nurses across 31 primary care practices, between June 2009 and December 2011 (Figure 1).

Baseline characteristics

Participant characteristics were well balanced between trial arms (Table 1). Participants were on average 49 years old, equally split between males and females, smoked 20 cigarettes daily, and had a Fagerstrom Test for Cigarette Dependence (FTCD) score of 6 (21), indicating high dependence. The majority of participants (94%) described their ethnicity as 'white'.

Abstinence rates

The primary outcome, 4-week Russell standard abstinence, was achieved by 39.2% (95% CI: 34.0, 44.4) of the Gradual arm and 49.0% (95%CI: 43.8, 54.2) of the Abrupt arm. Non-inferiority was not demonstrated (unadjusted RR 0.80; 90%CI: 0.68, 0.96). Rather at 4

weeks, achieving abstinence was significantly less likely for smokers in the Gradual arm than those in the Abrupt arm (adjusted RR 0.80, 95%CI 0.66, 0.93). The risk estimates for secondary outcomes, including six-month prolonged abstinence and point prevalence abstinence, also indicated superiority of abrupt over gradual cessation (Table 2). Excluding the second member of a couple gave similar RRs for abstinence at four weeks and six months (data not shown).

Visit attendance and adherence

Similar percentages of participants in the two arms attended the week -1 visit; (82% (n=279/342) of the gradual arm and 85.6% (n=304/355) of the abrupt arm (p=0.147)). However, significantly fewer participants in the gradual arm attended visit 0, immediately prior to quit day, (67.0% (n=229/342) versus 83.4% (n=296/355) in the abrupt arm; p<0.001). Fewer people made a quit attempt (at least 24 hours of self-reported abstinence) in the gradual arm (61.4%, n=210/342) than the abrupt arm (71%; 252/355); p=0.007. Among participants who made an attempt, relapse rates were similar in both arms at four week (gradual 36.2% (n=76/210); abrupt 31.0% (n=78/252); p=0.28) and six month (gradual 74.8% (n=157/210); abrupt 69.1% (n=174/252); p=0.21) follow-up.

Participants in the gradual arm cut their cigarette consumption by an average of 48% (target of 50%) after one week (visit -1) (n=264), and by 68% (target of 75%) at visit 0 (n=184). Exhaled carbon monoxide reduced by 32% at visit -1 (n=275) and by 46% at visit 0 (n=226). There were also modest reductions in cigarette consumption (n=237, 29%) and carbon monoxide (n=291, 18%) in the abrupt arm at visit 0 (Figure 2).

Medication adherence was generally good. Of those participants who attended visit -1, 81.4% (n=227/279) in the gradual arm and 89.5% (n=272/304) in the abrupt arm used their nicotine patch daily in the first week. Of those participants who attended visit 0, 87.3% (n=200/229) in the gradual arm and 89.2% (n=264/296) in the abrupt arm used their nicotine patch daily in the second week. Only participants in the gradual arm were provided with short-acting NRT pre-quit. In the first week 76.0% (n=212/279) used it and in the second week 76.0% (n=174/229) did so. Of the participants who used short-acting NRT, 84% (n=225/279) chose gum, lozenge, or sublingual tablets. Although the instruction was to replace each missed cigarette with one dose of these products, the mean dose was 2.8 (SD=3.1) units per day in the first week (on average participants reduced their smoking by 11 cigarettes per day), and 4.7 (SD=3.9) units per day in the second week (average reduction of 15 cigarettes per day). The dose of inhalator and nasal spray in the remaining participants was similarly low.

Post-quit urges and withdrawal symptoms

Withdrawal and urge scores were available on at least one assessment for 692 (99.3%) and 695 (99.7%), respectively. Over the whole four weeks there was no evidence of a difference between arms in withdrawal or urge intensity (withdrawal: p=0.29, urge: p=0.154), both of which declined over time. At week 4, there were no significant differences between arms in withdrawal (mean difference: 0.08; 95%CI: -0.03, 0.19) and urge (mean difference: 0.05; 95%CI: -0.06, 0.17) scores.

Intervention preference

At baseline, 16.9% (n=118) of participants had no preference for which intervention they were assigned, 32.1% (n=224) would have chosen abrupt quitting and 50.9% (n=355) gradual. Participants who preferred gradual cessation were significantly less likely to be abstinent at 4

weeks than those who preferred abrupt cessation (38.3% vs 52.2%; p=0.007). However, being allocated to quit abruptly, against their preference, was associated with an increase in abstinence at 4 weeks (42.0% versus 34.6% who were assigned to gradual cessation), albeit not significantly (p=0.152). The relative risks of achieving abstinence for the gradual cessation arm compared with the abrupt arm stratified by baseline preference were: prefer gradual RR=0.82 (95%CI: 0.64, 1.07), no preference 0.80 (95%CI: 0.49, 1.07), and prefer abrupt 0.79 (95%CI: 0.60, 1.08) (Table 3). Of all participants who did not achieve four week abstinence, 61% (N=112/184) said they would prefer to quit by reduction in a future quit attempt.

Adverse events

None of the serious adverse events reported during the trial were deemed a reaction to the trial medication. Three (shoulder arthroscopy; hospitalisation due to salivary gland calculus; hospitalisation for ovarian cyst) in the gradual cessation arm and one in the abrupt arm (orchidectomy) occurred whilst participants were using NRT and concurrently smoking. In participants who adhered to their NRT while still smoking, most symptoms of nicotine overdose were uncommon, mild and did not differ by arm (Supplement; Table A). Watering mouth and cold sweats were more common in the gradual than the abrupt arm in both pre-quit weeks.

Discussion

There was clear evidence that quitting abruptly was superior in the short and longer term. Adherence to behavioural instructions and pre-quit NRT was good, and medication well tolerated. People who preferred to quit gradually were less likely to succeed in achieving

abstinence regardless of how they were allocated to quit; being allocated to quit abruptly, against their preference, was associated with improved success.

Potential explanation and comparison of findings

A recent review (9) compared gradual and abrupt cessation approaches and found similar quit rates, with a summary RR of 0.94 (95%CI: 0.79, 1.13); whereas our data show superior results with abrupt cessation. We found evidence that gradual cessation was less successful than abrupt cessation probably because fewer people made a quit attempt when reducing smoking first. Another similar study reported that gradual cessation seemed to deter people from making quit attempts and also reported a substantial though not statistically significant advantage of abrupt cessation over gradual (22). Population data show that unaided abrupt quit attempts are twice as successful as quit attempts made by reducing first (5,8). One explanation could be that gradual cessation requires structure, for example a quit date or reduction goals, to maximise success (23). People quitting unsupported may not provide this structure for themselves. Another could be that motivation to quit predicts the means by which people quit, with those less motivated selecting gradual cessation (24,25), which is supported here by the fact that those who favoured gradual cessation at baseline were less likely to quit than those who favoured abrupt quitting, regardless of allocation.

Strengths

The use of NRT prior to quitting makes reduction more successful (13), but also may enhance the success of cessation regardless of whether reduction occurs; so we balanced any effect NRT may have had by offering it to both trial arms. We also guided participants on how to reduce their cigarettes using structured plans, which seems to enhance the success of reduction and

subsequent cessation (23). These two elements combined to ensure that we gave gradual cessation the best possible chance to succeed.

Limitations

Blinding was impossible; however there is no reason to believe that false claims of abstinence would have differed between arms, and the use of biological verification mitigates this further. Twenty three percent of the English population aged 18 and older are from a minority ethnic group and most ethnic minority groups have a much lower smoking prevalence than the majority population(27). Consequently non-white groups formed only 6% of the trial population and the results may not apply to groups other than white British, although we can think of no mechanism that might explain effect modification by ethnic group.

Implications and conclusions

Evidence that gradual is as successful as abrupt cessation would allow smoking cessation programmes to adopt this method and allow participants to choose, as suggested in guidelines on tobacco harm reduction from one country (28). These results imply that, in clinical practice, we should encourage people to stop smoking abruptly and not gradually. However, gradual cessation programs could still be worthwhile if they increase the number of people that try to quit or take up support and medication whilst trying. We need population-focused trials to assess the population impact of promoting and supporting a wider range of quitting options and programs than most countries currently support (29). However, key future developments will be finding means to retain smokers in gradual cessation programmes while they reduce, more successful reduction methods, or aborting reduction before participants deem it a failure and abandon their quit attempt. For now, however, we conclude that supporting gradual cessation

may be a useful way to increase cessation in the population, but abrupt quitting is the more effective method, even in people who have a preference against it.

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Competing interests

(2) NLH reports personal fees from manufacturers of smoking cessation aids, outside the submitted work; and manages an National Institute for Health Research, Health Technology Assessment programme funded trial of nicotine patch preloading. The nicotine patches for the trial are provided free of charge to the NHS by GlaxoSmithKline (GSK). GSK have no other involvement in the trial; (3) MB has nothing to disclose; (4) RW reports grants from Cancer Research UK, during the conduct of the study; grants from Pfizer, grants from Johnson&Johnson, personal fees from Pfizer, outside the submitted work; and is Honorary Director of the National Centre for Smoking Cessation and Training and trustee of the

charity, QUIT; (5) SM has nothing to disclose; (6) BS has nothing to disclose (7) PA reports grants from the UK Centre for Tobacco and Alcohol Studies and grants from the National Institute for Health Research School for Primary Care Research, during the conduct of the study; personal fees from Pfizer outside the submitted work, and is chief investigator of the preloading trial NLH manages.

Contributions

NLH was involved in the design of the study and literature search, carried out data analysis and data interpretation and drafted the manuscript, tables and figures. MB was involved in study data collection, cleaning the data and data-analysis, and drafting the manuscript. RW and SM were involved in designing the study and drafting the manuscript. BS was involved with and carried out data- analysis, and helped draft the manuscript. PA designed the study and was involved in the literature search, data collection, data analysis, data interpretation and drafting the manuscript tables and figures. NLH and PA are the study guarantors and had full access to all the study data, take responsibility for the integrity of the data and the accuracy of the analyses, and had final responsibility for the decision to submit for publication. They affirm that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. All authors had full access to all of the data in the study.

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Data sharing

Dataset available from corresponding authors on request.

References

1. Cinciripini PM, Lapitsky L, Seay S, Wallfisch A, Kitchens K, Van Vunakis H. The effects of smoking schedules on cessation outcome: can we improve on common methods of gradual and abrupt nicotine withdrawal? *Journal of Consulting & Clinical Psychology* 1995, 63: 388-399
2. Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, et al. *Treating tobacco use and dependence: 2008 update*. Rockville, MD: Department of Health and Human Services, 2008. (Accessed September 19, 2013, at http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/treating_tobacco_use08.pdf)
3. New Zealand Ministry of Health. *New Zealand smoking cessation guidelines.* Wellington: Ministry of Health, 2007. (Accessed March 16, 2015 at http://www.treatobacco.net/en/uploads/documents/Treatment%20Guidelines/New%20Zealand%20treatment%20guidelines%20in%20English%202007.pdf)
4. Society for Research on Nicotine and Tobacco. *National treatment guidelines.* Online: Wisconsin, USA, 2012. (Accessed September 19, 2013 at http://www.treatobacco.net/en/page_224.php)

5. Cheong Y, Yong H, Borland R. Does how you quit affect success? A comparison between abrupt and gradual methods using data from the international tobacco control policy evaluation study. *Nicotine & Tobacco Research* 2007; **9** (8): 801–810
6. Hughes JR. Smokers who choose to quit gradually versus abruptly. *Addiction* 2007; 102(8):1326–7
7. West R. *Behaviour change in theory and in real life.* London, UK 2008. (Accessed September 19, 2013, at www.rjwest.co.uk/downloadfile.php?filename=uploads/080424stockholm.ppt)
8. West R, Brown J *Smoking and Smoking Cessation in England 2011*. London, UK 2012. (Accessed September 19, 2013, at www.smokinginengland.info/downloadfile/?type=sts-documents&src=19)
9. Lindson-Hawley N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. *Cochrane Database of Systematic Reviews* 2012, Issue 11. Art. No.: CD008033
10. Blalock JA, Cinciripini PM, Crivens M. *Transdermal nicotine and gradual reduction for smoking cessation.* Presented at SRNT Annual Conference 2001: Seattle, USA
11. Haustein KO, Batra A, Landfeldt B, Westin A. The effect of short-term or long-term reduction on smoking cessation; results from a placebo controlled smoking reduction study with the nicotine gum.Nicotine and Tobacco Research. 2003;5:278.
12. McEwen A. *Standard treatment programme: one-to-one smoking cessation support*. London, UK: National Centre for Smoking Cessation and Training 2012. (Accessed September 20, 2013, at http://www.ncsct.co.uk/usr/pub/NCSCT%20STP.pdf)
13. Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* 2009, 338: 867-880

14. Shiffman S, Ferguson SG. Nicotine patch therapy prior to quitting smoking: a meta-analysis. *Addiction* 2008, 103: 557-563

15. Hajek P. Withdrawal-oriented therapy for smokers. *British Journal of Addiction* 1989, 84: 591-598

16. The NHS Information Centre. *Key facts on NHS Stop Smoking Services in England, April 2010 to September 2010.* Leeds, UK 2011. (Accessed September 19, 2013, at https://catalogue.ic.nhs.uk/publications/public-health/smoking/nhs-stop-smok-serv-eng-2010-q2-rep/nhs-stop-smok-serv-eng-2010-q2-rep-key-apx.pdf)

17. West R, Hajek P. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology (Berl)* 2004, 177: 195-199

18. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005, 100: 299-303

19. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, for the CONSORT Group. Reporting of noninferiority and equivalence randomized trials. Extension of the CONSORT 2010 statement. *JAMA* 2012; 308(24): 2594-2604

20. Localio AR, Margolis DJ, Berlin JA. Relative risks and confidence intervals were easily computed indirectly from multivariable logistic regression. J Clin Epidemiol. 2007 Sep;60(9):874-82. Epub 2007 Jan 18.

21. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction* 1991, 86: 1119-1127.

22. Hughes JR., Solomon LJ., Livingston AE., Callas PW, & Peters EN. (2010). A randomized, controlled trial of NRT-aided gradual vs. abrupt cessation in smokers actively trying to quit. *Drug and Alcohol Dependence*,*111*(1), 105-113.

23. Cinciripini PM, Lapitsky L, Seay S, Wallfisch A, Kitchens K, Van Vunakis H. The effects of smoking schedules on cessation outcome: can we improve on common methods of gradual and abrupt nicotine withdrawal? *Journal of Consulting & Clinical Psychology* 1995, 63: 388-399.

24. Wee LH, Shahab L, West R, Bulgiba A. Conflict about quitting predicts the decision to stop smoking gradually or abruptly: Evidence from stop smoking clinics in Malaysia. *Journal of Smoking Cessation* 2011, 6: 37-44.

25. Peters EN, Hughes JR, Callas PW, Solomon LJ. Goals indicate motivation to quit smoking. *Addiction* 2007;102:1158-63

26. Foulds J, Stapleton J, Hayward M, Russell MA, Feyerabend C, Fleming T, Costello J. Transdermal nicotine patches with low-intensity support to aid smoking cessation in outpatients in a general hospital. A placebo-controlled trial. *Archives of Family Medicine* 1993:2;417–423.

27. Office for National Statistics. Health Survey for England 2004: the Health of Minority Ethnic Groups- headline tables. Health and Social Care Information Centre, 2005. Accessed 27 May at http://www.hscic.gov.uk/catalogue/PUB01209/heal-surv-hea-eth-min-hea-tab-eng-2004-rep.pdf.

28. NICE Public Health Guidance 45. *Tobacco: harm-reduction approaches to smoking.* London, UK 2013. (Accessed March 16, 2015 at http://www.nice.org.uk/guidance/ph45/resources/guidance-tobacco-harmreduction-approaches-to-smoking-pdf)

29. Aveyard P, Lindson-Hawley N, Hastings G, de Andrade M. Should smokers be advised to cut down as well as quit? BMJ 2014: 348:g2787

551**Table 1 Participant baseline characteristics**

Characteristic	All (N=697)[a]	Gradual cessation (N=342)[a]	Abrupt cessation (N=355)[a]
Age, median (IQR)	49.0 (17.0)	49.0 (17.3)	49.0 (17.0)
Male gender, n/N (%)	350/697 (50.2)	175/342 (51.2)	175/355 (49.3)
White ethnicity, n/N (%)	648/692 (93.6)	319/341 (93.5)	329/351 (93.7)
Post-secondary school (15/16 years) educational qualification, n/N (%)	345/678 (50.9)	160/330 (48.5)	185/348 (53.2)
In paid employment, n/N (%)	382/691 (55.3)	190/340 (55.9)	192/351 (54.7)
Age started smoking (years), median (IQR)	16.0 (4.0)	16.0 (3.0)	16.0 (4.0)
Lives with smoker, n/N (%)	266/688 (38.7)	116/335 (34.6)	150/353 (42.5)
Number of previous quit attempts, median (IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (3.0)
Type of cigarettes smoked **-Smokes manufactured cigarettes, n/N (%)** **-Smokes hand-rolled cigarettes, n/N (%)** **-Smokes both manufactured and hand-rolled cigarettes, n/N (%)**	 530/697 (76.0) 137/697 (19.7) 30/697 (4.3)	 266/342 (77.8) 61/342 (17.8) 15/342 (4.4)	 264/355 (74.4) 76/355 (21.4) 15/355 (4.2)
Number of cigarettes per day, median (IQR)	20.0 (10.0)	20.0 (10.0)	20.0 (9.0)
Expired carbon monoxide concentration (ppm), median (IQR)	24.0 (14.0)	24.0 (14.0)	24.0 (14.0)
Salivary cotinine concentration (ng/ml), median (IQR)	358.5 (212.7)	365.3 (234.5)	349.5 (197.7)
FTCD score, median (IQR)	6.0 (3.0)	6.0 (3.0)	6.0 (3.0)

Preference for abrupt arm, n/N (%)	224/697 (32.1)	107/342 (31.3)	117/355 (33.0)
Preference for reduction arm, n/N (%)	355/697 (50.9)	179/342 (52.3)	176/355 (49.6)
No trial arm preference, n/N (%)	118/697 (16.9)	56/342 (16.4)	62/355 (17.5)
Confidence in quitting, median (IQR)[c]	4.0 (1.0)	4.0 (1.0)	4.0 (1.0)

552 n/N=number of participants; IQR=interquartile range; ppm=parts per million; ng/ml=nanograms per millileter;
553 FTCD=Fagerstrom Test for Cigarette Dependence
554 [a]Numbers of participants used to calculate statistics for each variable vary slightly in some cases due to missing
555 data (denominators provided); [b]Range from 0 to 10, where 10=highest level of dependence; [c]Measured on a
556 scale from 1 to 6, where 1=Very low and 6=Extremely high
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Table 2 Abstinence Outcomes

Abstinence outcome	Number Abstinent (%)		Absolute difference % (95%CI)	Relative Risk (95%CI) [b]
	Gradual cessation arm (N=342)	Abrupt cessation arm (N=355)		
Prolonged CO validated[a]				
RS abstinence at 4 weeks post-quit	134 (39.2)	174 (49.0)	9.8 (2.5 to 17.1)	0.80 (0.66 to 0.93)
RS abstinence at 8 weeks post-quit	100 (29.2)	130 (36.6)	7.4 (0.4 to 14.3)	0.80 (0.63 to 0.95)
RS abstinence at 6 months post-quit	53 (15.5)	78 (22.0)	6.5 (0.7 to 12.2)	0.71 (0.46 to 0.91)
7 day point prevalence[c], CO validated[a]				
4 week	146 (42.7)	191 (53.8)	9.1 (1.8 to 16.5)	0.83 (0.72 to 0.98)
8 week	106 (31.0)	136 (38.3)	7.3 (0.3 to 14.3)	0.81 (0.68 to 1.04)
6 month	63 (18.4)	94 (26.5)	8.1 (1.9 to 14.2)	0.70 (0.51 to 0.97)
Self-reported				
24 hour	210 (61.4)	252 (71.0)	9.6 (2.6 to 16.5)	0.87 (0.77 to 0.97)

RS= Russell Standard; N=number of participants; CO=carbon monoxide; CI=confidence interval

[a]Validated by a carbon monoxide reading of <10 parts per million
[b]Adjusted for nurse
[c]No smoking in the 7 days prior to assessment

Table 3 Russell standard 4-week quit rates stratified by baseline trial arm preference and trial arm allocation

Baseline preference for quitting method	Trial arm to which participant allocated		
	Gradual cessation (N=342)	Abrupt cessation (N=355)	Total (N=697)
	n (%) abstinent at 4 weeks	n (%) abstinent at 4 weeks	n (%) abstinent at 4 weeks
Preferred abrupt arm (N=224)	49/107 (45.8%)	68/117 (58.1%)	117/224 (52.2)
Preferred reduction arm (N=355)	62/179 (34.6%)	74/176 (42.0%)	136/355 (38.3)
No preference (N=118)	23/56 (41.1%)	32/62 (51.6%)	55/118 (46.6)

Figure 1: Participant flow through the Rapid Reduction Trial (RRT)

Figure 2: Mean (95% CI) pre-quit exhaled carbon monoxide (CO) and cigarettes per day (cpd) split by trial arm

Figure 2 Legend: Cpd=cigarettes per day; CO=carbon monoxide; ppm=parts per million Gradual cpd Ns (baseline n=342; visit -1 n=264; visit 0 n=184). Gradual CO Ns (baseline n=342; visit -1 n=275; visit 0 n=226). Abrupt cpd Ns (baseline n=355; visit -1 n=299; visit 0 n=237). Abrupt CO Ns (baseline n=354; visit -1 n=299; visit 0 n=292).

601 Figure 1.
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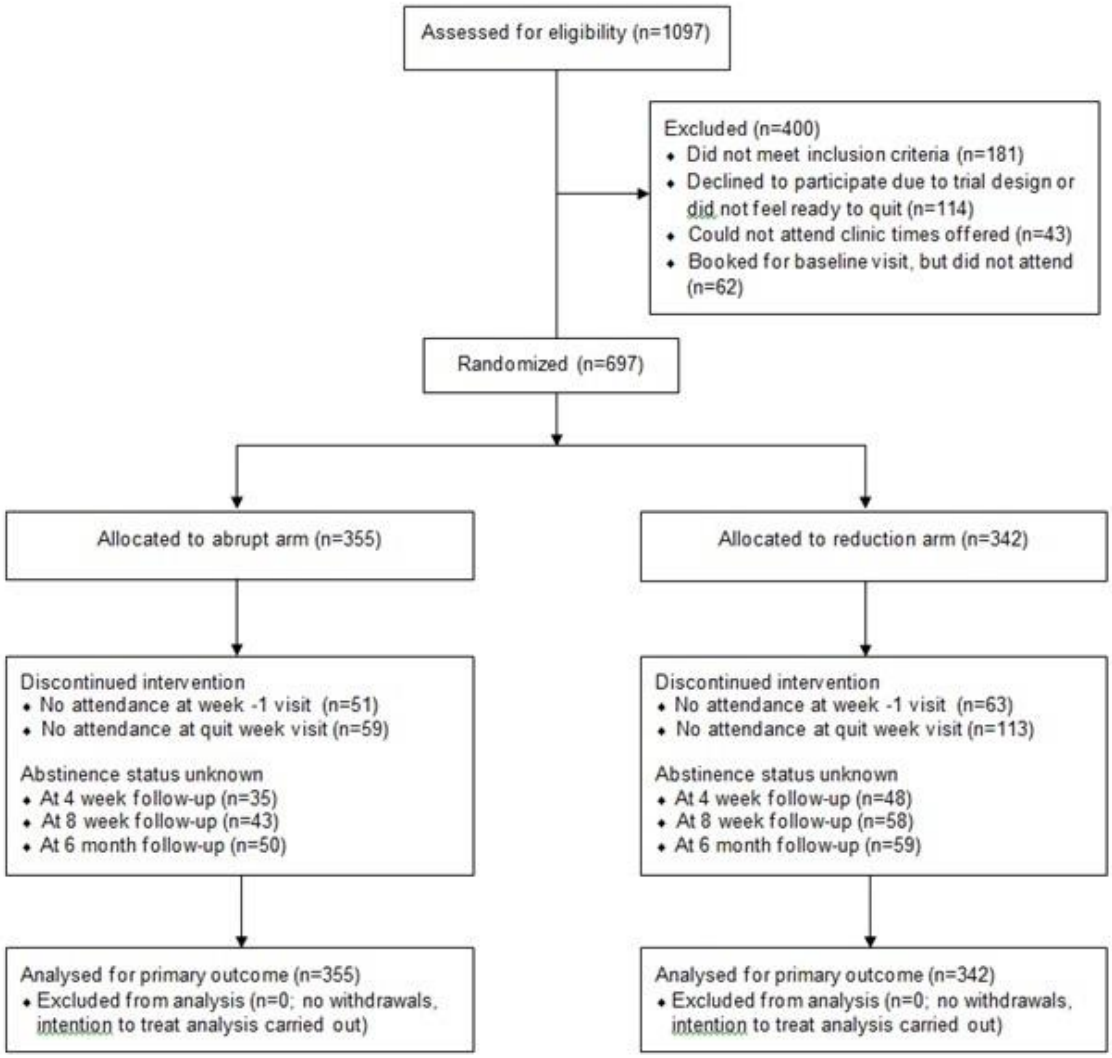

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605 Figure 2.
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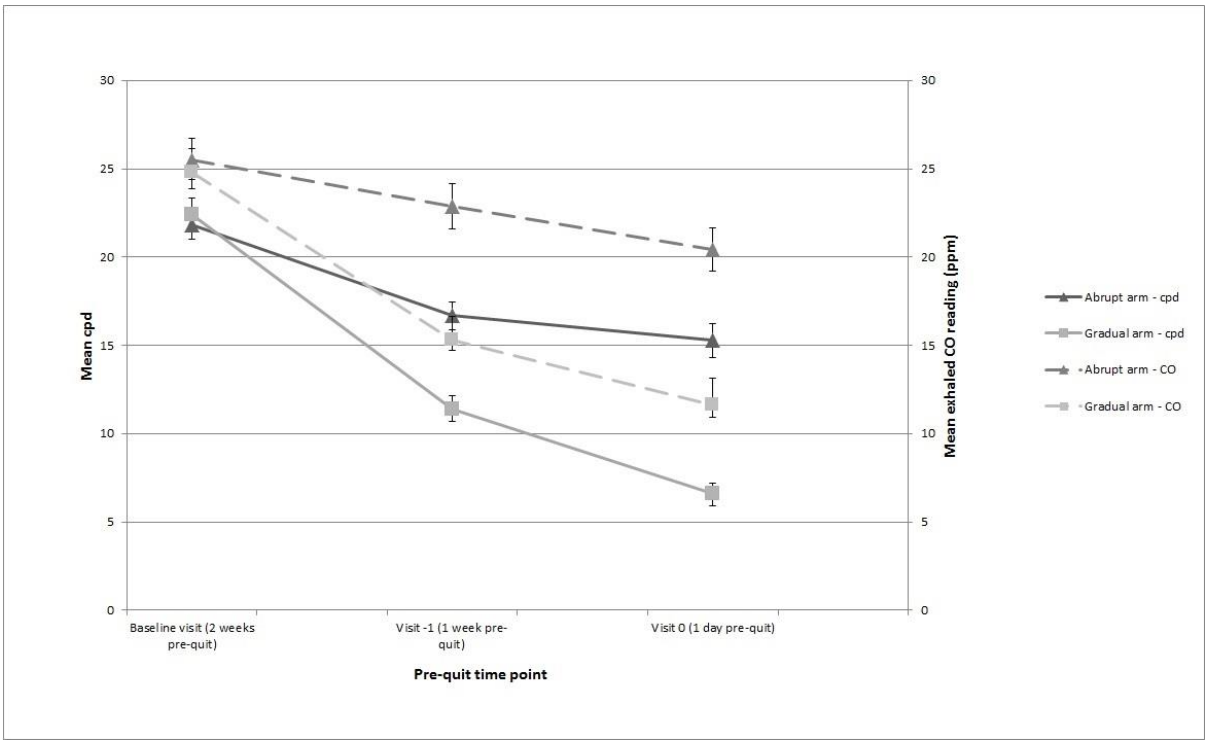

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