Nicotine and nicotine replacement therapy – the facts

by Professor Nick Zwar, MBBS, PhD, Professor of General Practice, School of Public Health and Community Medicine, University of New South Wales

**John Bell, AM BPharm, Principal Adviser, Pharmacy Self Care, Pharmaceutical Society of Australia*

Professor Matthew Peters, MD, Chairman, Action on Smoking and Health

Professor MacDonald Christie, PhD Faculty of Medicine, University of Sydney and Consultant Pharmacologist, Royal North Shore Hospital

Dr Colin Mendelsohn, MBBS (Hons), General Practitioner, Kingsford, Editor, Your Health newsletter

**Author for correspondence: john.bell@hcn.net.au*

There are many misperceptions about the role of nicotine in the harmful effects of smoking on health. Surveys of Australian smokers suggest that these misperceptions result in a significant number of smokers both delaying quit attempts and avoiding quitting with clinically proven nicotine replacement therapy.

This review addresses the common myths or misperceptions surrounding nicotine by summarising the available evidence on the role of nicotine and the safety of nicotine replacement therapy.

Introduction

There are many misperceptions about the role of nicotine in the harmful effects of smoking on health.[1] A survey of Australian smokers found that 25% believed that nicotine replacement therapy (NRT) was just as harmful as smoking cigarettes and an additional 40% of smokers did not know whether this was true or false.[1] These misperceptions result in a significant number of smokers both delaying quit attempts and quitting unassisted,[1] which is less effective than quitting with proven aids like NRT.[2]

The effectiveness of NRT in aiding cessation is well established and is supported by the highest level of clinical evidence,[2,3] systematic review of more than 90 randomised clinical trials.[2] Smoking cessation guidelines from Australia and overseas recommend that all smokers be offered pharmacotherapy to assist quitting, unless contraindicated, and recommend NRT as a first-line therapy.[3,4] Guidance from the National Prescribing Service notes the equivalent efficacy of NRT and bupropion on current evidence but recommends NRT be used first, given its more extensive clinical experience and superior safety profile.[5] By combining NRT with behavioural support, success rates can be further improved.[6] Nicotine replacement therapy is not only effective it is also cost effective, at a daily cost that is approximately half that of smoking cigarettes, and when NRT is stopped the typical smoker will save in the order of $3000 per year by not purchasing cigarettes.

This review addresses the common myths or misperceptions surrounding nicotine by summarising the available evidence on the role of nicotine and the safety of nicotine replacement therapy.

Myth 1: Nicotine is the most harmful ingredient in cigarettes

Fact: Cigarette smoke contains over 4000 compounds and it is these other toxins, not nicotine, that are responsible for tobacco-related diseases.

Smoking tobacco is the leading cause of preventable disease and death in Australia. Smoking harms nearly every organ in the body, causing many diseases including many cancers, chronic respiratory illnesses, and cardiovascular disease.[7]

The most important action of nicotine in cigarettes is the maintenance of addiction.[8] It is the myriad of other toxins in cigarette smoke that are responsible for the majority of harmful effects of smoking.[8]

Nicotine has not been shown to be carcinogenic.[8] It has not been implicated in the development of chronic respiratory diseases.[8] Although nicotine has haemodynamic effects that may play some role in increasing the risk of heart disease, it is not a major cardiac risk factor.[8] The use of nicotine replacement therapy (NRT) is not associated with increase risk of cardiovascular events.[9-11]

Table: Nicotine myths and facts

Myth	Fact
1. Nicotine is the most harmful ingredient in cigarettes	Nicotine is not directly responsible for tobacco-related diseases. The only important actions of nicotine in cigarettes are the induction and maintenance of addiction. Nicotine is not carcinogenic, does not cause respiratory diseases and is not a major cause of cardiac risk associated with smoking.
2. Nicotine causes cancer	Nicotine is not carcinogenic. There is no clinical evidence that NRT is associated with an increased risk of developing cancer.
3. Nicotine causes cardiovascular disease	Nicotine does have haemodynamic effects however it is not the major cause of increased cardiac risk associated with smoking. NRT can be safely used as a cessation aid in patients with stable cardiac conditions, including angina and previous myocardial infarction.
4. Smoking while using nicotine replacement therapy is unsafe and increases the risk of heart attack.	Smoking whilst using nicotine replacement therapy does not increase the risk of a heart attack or related cardiovascular events as tolerance to the haemodynamic effects of nicotine develops acutely.
5. Using more than one form of nicotine replacement is unsafe	Combining more than one form of NRT can be used safely to assist people quit smoking. Clinical trials have demonstrated no significant increase in adverse events when more than one form of NRT is used concurrently in suitable smokers.
6. Nicotine replacement therapy is as addictive as cigarettes	Nicotine from cigarettes is addictive because it is delivered rapidly from smoke. All forms of NRT deliver nicotine slowly and have low or no abuse potential.
7. Nicotine replacement therapy is just as harmful as smoking during pregnancy	NRT is safer than continuing smoking during pregnancy and has the potential to improve birth outcomes.
8. Nicotine replacement therapy is just as harmful as smoking while breastfeeding	The use of NRT while breastfeeding is unlikely to be hazardous and is safer than continuing smoking as it reduces infant exposure to cigarette smoke.
9. Nicotine replacement therapy is not safe for use by adolescent smokers	NRT can be safely used by adolescent smokers to help them quit. The adverse event profile of NRT in adolescents is the same as in adults. NRT should be considered as a cessation aid by adolescent smokers who are daily smokers and who are motivated to quit.

The available evidence can be summarised under the following statement:
Using nicotine replacement therapy to quit is always safer than continuing to smoke.

Myth 2: Nicotine causes cancer

Fact: Nicotine is not carcinogenic. There is no clinical evidence that NRT is associated with an increased risk of developing cancer.

Smoking tobacco is a leading cause of cancer.[7] Tobacco smoke contains more than 50 known carcinogens including nitrosamines.[7] There is substantial evidence that nitrosamines cause many human cancers.[8] Nicotine has not been shown to be carcinogenic in animals and to date there is no evidence that NRT causes cancer in humans.[8] Nicotine could theoretically contribute to an increased cancer risk via metabolism to form carcinogenic nitrosamines[12] or by promoting tumour growth,[13] however it appears extremely unlikely that nicotine is capable of stimulating cancer under normal conditions.[14]

Evidence supporting the long term safety of nicotine comes from epidemiological studies of Swedish snus use, an oral smokeless tobacco product. These studies found no increased risk of lung cancer,[15] oral cancer,[14-17] gastric cancer,[15,17] kidney cancer[14] or head and neck cancers.[18] One study of snus use has found an increased risk of pancreatic cancer, however the authors attributed this excess risk to nitrosamine content and not nicotine.[17]

Myth 3: Nicotine causes cardiovascular disease (e.g. myocardial infarcts and strokes)

Fact: Smoking is a leading cause of heart disease and strokes. Nicotine does have haemodynamic effects however it is not the major cause of increased cardiac risk. NRT is safe to use as a cessation aid in patients with stable cardiac conditions, including angina and previous myocardial infarction.

Smoking is a leading cause of heart disease and strokes.[7] Nicotine has pharmacological effects on the cardiovascular system resulting in increased heart rate and blood pressure and it can cause coronary artery vasoconstriction.[19,20] However cigarette smoking is more hazardous as, unlike smoking, nicotine alone does not lower oxygen carrying capacity, activate coagulation or lead to arterial disease.[19,20]

The safety of NRT in patients with cardiovascular disease is well supported by evidence from meta-analysis,[10] clinical trials,[11,21-25] observational[26-28] and physiological studies.[29-32] The evidence is that NRT is not associated with an increased risk of myocardial infarct or adverse cardiovascular outcomes.[9,10,27] Cardiovascular risk factors improve overall with smoking cessation that is accomplished with NRT,[21] and NRT appears safe even when used with high doses of transdermal patch,[32] combination NRT[21] or whilst continuing smoking.[11, 30]

NRT has not been well studied in acutely ill cardiac patients and patients with unstable cardiac conditions. The studies that have been done have not shown an increase in risk of vascular events.[11,33] The slower delivery rates and lower levels of nicotine with NRT suggest that NRT is safer than continuing smoking in these patients.[19]

Myth 4: Smoking while using nicotine replacement therapy is unsafe and increases the risk of heart attack.

Fact: Smoking whilst using nicotine replacement therapy does not significantly increase the risk of a heart attack or related cardiovascular events.

It is advised that people using NRT cease smoking while using NRT to minimise the risk of adverse events associated with high doses of nicotine, such as nausea and vomiting, as well as to increase the rate of successful quitting rather than any specific cardiovascular risk.

Smoking whilst using NRT does not pose a significant additional cardiovascular risk than that posed by smoking alone. Physiological studies, including one study of wearing up to three 21mg nicotine patches whilst smoking, have demonstrated that tolerance develops acutely to the haemodynamic effects of nicotine, such that further increases in nicotine concentrations from the use of NRT does not further increase heart rate, blood pressure or other cardiovascular effects compared to smoking alone.[30,32]

Myth 5: Using more than one form of nicotine replacement is unsafe

Fact: Combining more than one form of NRT can be used safely to assist people during a quit smoking attempt.

There are only a small number of clinical trials of the combined use of more than one form of NRT.[2] These clinical trials indicate that combination therapy can be more effective than a single form of NRT for some patients. These trials have not shown any significant increase in adverse events to suggest that this practice is unsafe.[21,32,34,35]

Myth 6: Nicotine replacement therapy is as addictive as cigarettes

Fact: Nicotine replacement therapy has a low abuse potential. Nicotine patches have negligible addictive potential and oral forms of NRT are significantly less addictive than cigarettes.

Nicotine can be highly addictive with its addictive potential varying according to the rate and route of administration.[8] Inhalation of nicotine through cigarettes is the most addictive method of nicotine delivery as:

- It takes only 10-19 seconds for the nicotine absorbed from the lungs to reach the brain.[8]
- Peak blood nicotine levels are achieved within seconds and then decline rapidly; and this pattern is repeated and reinforced with every inhalation.[8]

Nicotine replacement therapy does not produce the rapid, high levels of nicotine in the blood as obtained from smoking. The rise in blood nicotine levels is slower and the level of fluctuation is decreased. Oral forms of NRT, e.g. gum, deliver nicotine at a rate faster than patch but much slower than from a cigarette. Nicotine gum and lozenges have a low addictive potential although it is higher than for NRT patches which has almost no addictive potential.[8]

Myth 7: Nicotine replacement therapy is just as harmful as smoking during pregnancy

Fact: Nicotine replacement therapy is safer than continuing smoking during pregnancy and has the potential to improve birth outcomes.

The harmful effects of smoking during pregnancy are well-established and include an increased risk of miscarriage, premature births and low-weight babies.[36] While nicotine may play a part with some of the risks to the foetus by contributing to foetal ischemia, hypoxia[36, 37] and potentially influencing CNS development,[37] overall NRT is considered to be safer than continuing to smoke as cigarette smoke contains other known foetal toxins as well as nicotine.[36,38]

Systematic reviews of smoking cessation during pregnancy have clearly demonstrated that smoking cessation is associated with improved birth outcomes including a reduction in preterm birth and an increase in birth weight.[39,40]

Experience with NRT in pregnant women is limited. To date, NRT use has not been associated with significant clinical problems for the mother or child,[37, 41,42] however its effectiveness to assist quitting has also not been established.[43-45] Given the need to protect the unborn baby from cigarette smoke and the proven effectiveness of NRT in the general population,[2] NRT should be considered for use by pregnant smokers who don't believe they would be able to quit without its assistance.

Myth 8: Nicotine replacement therapy is just as harmful as smoking while breastfeeding

Fact: The use of nicotine replacement therapy while breastfeeding is unlikely to be hazardous and is safer than continuing smoking as it reduces infant exposure to cigarette smoke.

The risks of smoking to babies is well documented and includes an increased risk of neonatal mortality and sudden infant death syndrome (SIDS).[7]

Nicotine from smoking and NRT can pass to the baby through breast milk,[37,46] however infant exposure to nicotine is estimated to be about 50 times less than maternal exposure and is unlikely to be hazardous.[37] The use of NRT whilst breastfeeding could reduce infant exposure to cigarette smoke that is known to be hazardous.[37]

There is no evidence to favour one form of NRT in preference to another for women breastfeeding, hence the selection of which form of NRT to quit with should be based on patient preference and previous quitting experience.

Myth 9: Nicotine replacement therapy is not safe for use by adolescent smokers

Fact: Nicotine replacement therapy can be safely used by adolescent smokers to help them quit.

Most people commence smoking whilst they are teenagers; however there have been very few studies on how to assist adolescent smokers to quit.

To date there are only four published studies on the use of NRT amongst adolescent smokers. The data suggests that NRT patches and gum are well tolerated by adolescent smokers with adverse events reported matching those seen amongst adult smokers.[47-50]

The efficacy of NRT amongst adolescent smokers from these studies has not been well established in part due to the limited size of the studies. Six month abstinence rates of 5% were observed in the two open-label trials.[49,50] In a placebo controlled trial, Hanson, *et al.* demonstrated that nicotine patches reduced cravings and withdrawal symptoms, however the quit rate of 28% at 10 weeks was not significantly different to placebo.[48] In contrast Moolchan, *et al.* demonstrated higher abstinence rates for nicotine patches (17.7% vs 2.5% placebo, p=0.043), however the abstinence rate for nicotine gum (6.5%) was not statistically different to placebo.[47] A potential secondary benefit of using NRT was the reduction in the number of cigarettes smoked per day even amongst those adolescents who failed to achieve total abstinence.[48]

Given that the effectiveness of NRT is well established amongst adult smokers,[2] and that NRT appears to be well tolerated amongst adolescent smokers, NRT should be considered as a cessation aid by adolescent smokers who are daily smokers and who are motivated to quit.

Conclusion

The safety profile of nicotine replacement therapy is well established and the available evidence can be summarised under the following statement: using nicotine replacement therapy to quit is always safer than continuing to smoke.

Nicotine replacement therapy continues to be a first-line smoking cessation therapy and it has an expanding role in assisting previously considered special patient populations to quit smoking.

Conflict of interest

This review was developed by an expert panel convened by GlaxoSmithKline Consumer Healthcare. The authors would like to thank George Krassas of Scius Solutions Pty Ltd for assistance in the preparation of this manuscript; whose contribution has been funded by an unrestricted educational grant from GlaxoSmithKline Consumer Healthcare.

References

1. GlaxoSmithKline Data on file. 2005.
2. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. BMJ 2000;321:355-8.
3. Zwar N, Richmond RL, Borland R, Stillman S, Cunningham M, Litt J. Smoking Cessation Guidelines For Australian General Practice. 2004.
4. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Clinical practice guidelines. 2000. Rockville, MD, US Department of Health and Human Services. Public Health Service.
5. National Prescribing Service. Prescribing Practice Review 20 Smoking Cessation. www nps org au 2002 October20. Available from: www.nps.org.au
6. www.treatobacco.net 2004 July 2 Available from: www.treatobacco.net
7. US Department of Health and Human Services. The health consequences of smoking: A report of the Surgeon General . US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2004.
8. Benowitz NL. Nicotine Safety and Toxicity. New York: Oxford University Press; 1998.
9. Hubbard R, Lewis S, Smith C, Godfrey C, Smeeth L, Farrington P, et al. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. Tob Control 2005 Dec;14(6):416-21.
10. Greenland S, Satterfield MH, Lanes SF. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. Drug Saf 1998 Apr;18(4):297-308.
11. Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. N Engl J Med 1996 Dec 12;335(24):1792-8.
12. Hecht SS, Hochalter JB, Villalta PW, Murphy SE. 2'-Hydroxylation of nicotine by cytochrome P450 2A6 and human liver microsomes: formation of a lung carcinogen precursor. Proc Natl Acad Sci USA 2000 Nov 7;97(23):12493-7.
13. Heeschen C, Jang JJ, Weis M, Pathak A, Kaji S, Hu RS, et al. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis. Nat Med 2001 Jul;7(7):833-9.
14. Foulds J, Ramstrom L, Burke M, Fagerstrom K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. Tob Control 2003 Dec;12(4):349-59.
15. Roth DH, Roth AB, Liu X. Health risks of smoking compared to Swedish snus. Inhal Toxicol 2005 Dec 1;17(13):741-8.
16. Schildt EB, Eriksson M, Hardell L, Magnuson A. Oral snuff, smoking habits and alcohol consumption in relation to oral cancer in a Swedish case-control study. Int J Cancer 1998 Jul 29;77(3):341-6.
17. Boffetta P, Aagnes B, Weiderpass E, Andersen A. Smokeless tobacco use and risk of cancer of the pancreas and other organs. Int J Cancer 2005 May 10;114(6):992-5.
18. Lewin F, Norell SE, Johansson H, Gustavsson P, Wennerberg J, Biorklund A, et al. Smoking tobacco, oral snuff, and alcohol in the etiology of squamous cell carcinoma of the head and neck: a population-based case-referent study in Sweden. Cancer 1998 Apr 1;82(7):1367-75.
19. McRobbie H, Hajek P. Nicotine replacement therapy in patients with cardiovascular disease: guidelines for health professionals. Addiction 2001;96:1547-51.
20. Benowitz NL. Cigarette smoking and cardiovascular disease: Pathophysiology and implications for treatment. Progress in Cardiovascular Diseases 2003;46(1):91-111.
21. Haustein KO, Krause J, Haustein H, Rasmussen T, Cort N. Comparison of the effects of combined nicotine replacement therapy vs. cigarette smoking in males. Nicotine Tob Res 2003 Apr;5(2):195-203.
22. Lúdvíksdóttir D, Blöndal T, Franzon M, Gudmundsson TV, Säwe U. Effects of nicotine nasal spray on atherogenic and thrombogenic factors during smoking cessation. J Intern Med 1999;246:61-6.
23. Benowitz NL, Fitzgerald GA, Wilson M, Zhang Q. Nicotine effects on eicosanoid formation and hemostatic function: comparison of transdermal nicotine and cigarette smoking [see comments]. J Am Coll Cardiol 1993 Oct;22(4):1159-67.
24. Tzivoni D, Keren A, Meyler S, Khoury Z, Lerer T, Brunel P. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. Cardiovasc Drugs Ther 1998 Jul;12(3):239-44.
25. Marsh HS, Dresler CM, Choi JH, Targett DA, Gamble ML, Strahs KR. Safety profile of a nicotine lozenge compared with that of nicotine gum in adult smokers with underlying medical conditions: a 12-week, randomized, open-label study. Clin Ther 2005 Oct;27(10):1571-87.
26. Broderick JP, Viscoli CM, Brott T, Kernan WN, Brass LM, Feldmann E, et al. Major risk factors for aneurysmal subarachnoid hemorrhage in the young are modifiable. Stoke 2003;34:1375-81.
27. Kimmel SE, Berlin JA, Miles C, Jaskowiak J, Carson JL, Strom BL. Risk of acute first myocardial infarction and use of nicotine patches in a general population. J Am Coll Cardiol 2001;37(5):1297-302.
28. Murray RP, Bailey WC, Daniels K, Bjornson WM, Kurnow K, Connett JE, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the lung health study. Chest 1996;109:438-45.
29. Basler HD, Brinkmeier U, Buser K, Gluth G. Nicotine gum assisted group therapy in smokers with an increased risk of coronary disease-evaluation in a primary care setting format. Health Educ Res 1992 Mar;7(1):87-95.
30. Keeley EC, Pirwitz MJ, Landau C, Lange RA, Hillis LD, Foerster EH, et al. Intranasal nicotine spray does not augment the adverse effects of cigarette smoking on myocardial oxygen demand or coronary arterial dimensions. Am J Med 1996 Oct;101(4):357-63.
31. Tanus-Santos JE, Toledo JC, Cittadino M, Sabha M, Rocha JC, Moreno H, Jr. Cardiovascular effects of transdermal nicotine in mildly hypertensive smokers. Am J Hypertens 2001 Jul;14(7 Pt 1):610-4.
32. Zevin S, Jacob P, Benowitz NL. Dose-related cardiovascular and endocrine effects of transdermal nicotine. Clin Pharmacol Ther 1998 Jul;64(1):87-95.
33. Meine TJ, Patel MR, Washam JB, Pappas PA, Jollis JG. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. Am J Cardiol 2005 Apr 15;95(8):976-8.
34. Blondal T, Gudmundsson LJ, Olafsdottir I, Gustavsson G, Westin A. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. BMJ 1999 Jan 30;318(7179):285-8.
35. Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. Arch Intern Med 2000 Nov 13;160(20):3128-34.
36. Benowitz NL. Nicotine replacement therapy during pregnancy. JAMA 1991;266(22):3174-7.
37. Dempsey DA, Benowitz NL. Risks and benefits of nicotine to aid smoking cessation in pregnancy. Drug Saf 2001;24(4):277-322.
38. Coleman T, Britton J, Thornton J. Nicotine replacement therapy in pregnancy is probably safer than smoking. BMJ 2004;328:965-6.
39. Anti-Cancer Council of Victoria. Smoking cessation in pregnancy. 2001.
40. Lumley J, Oliver S, Waters E. Interventions for promoting smoking cessation during pregnancy (Cochrane review). The Cochrane Library; 2005. Report No.: Issue 4.
41. Schroeder DR, Ogburn PL, Croghan IT, Ramin KD, Offord KP, Moyer TP. Nicotine patch use in pregnant smokers: smoking abstinence and delivery outcomes. j Maternal-Fetal Neonatal Med 2002;11:100-7.
42. Ogburn PL, Hurt RD, Croghan IT, Schroeder DR, Ramin KD, Offord KP, et al. Nicotine patch use in pregnant smokers: nicotine and contine levels and fetal effects. Am J Obst Gynecology 1999;181(3):736-43.
43. Wisborg K, Henriksen TB, Jespersen LB, Secher NJ. Nicotine patches for pregnant smokers: a randomized controlled study. Obstet Gynecol 2000 Dec;96(6):967-71.
44. Kapur B, Hackman R, Selby P, Klein J, Koren G. Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. Curr Ther Res Clin Exp 2001;62(4):274-8.
45. Hegaard HK, Kjaergaard H, Moller LF, Wachmann H, Ottesen B. Multimodal intervention raises smoking cessation rate during pregnancy. Acta Obstet Gynecol Scand 2003;82:813-9.
46. Ilett KF, Hale TW, Page-Sharp M, Kristensen JH, Kohan R, Hackett LP. Use of nicotine patches in breast-feeding mothers: transfer of nicotine and contine into human milk. Clin Pharmacol Ther 2003;74:516-24.
47. Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, et al. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics 2005 Apr;115(4):e407-e414.
48. Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch. Nicotine Tob Res 2003 Aug;5(4):515-26.
49. Hurt RD, Croghan GA, Beede SD, Wolter TD, Croghan IT, Patten CA. Nicotine patch therapy in 101 adolescent smokers: efficacy, withdrawal symptom relief, and carbon monoxide and plasma cotinine levels. Arch Pediatr Adolesc Med 2000 Jan;154(1):31-7.
50. Smith TA, House RFJ, Croghan IT, Gauvin TR, Colligan RC, Offord KP, et al. Nicotine patch therapy in adolescent smokers. Pediatrics 1996 Oct;98 (4 Pt 1):659-67.