Tobacco smoking: options for helping smokers to quit

Dear Editor

Zwar, Mendelsohn and Richmond's exclusive reliance on nicotine replacement therapy (NRT) clinical trial efficacy findings in their article 'Tobacco smoking: options for helping smokers to quit'[1] (*AFP* June 2014) leaves readers with the false impression that clinical efficacy has translated into population level effectiveness.

Doran et al 2006[2] involved a cross-sectional survey of 8333 Australian general practice patients. They found that cold-turkey quitting was roughly twice as effective as NRT. They also found that cold-turkey quitting accounted for 88% of all successful quitters (1942 of 2207).[2] More recently, a July 2013 US Gallup Poll found that only 8% of ex-smokers credited any quit smoking product (NRT or prescription medication) for their success.[3]

Imagine the assault on motivation endured by the average patient attempting to quit cold turkey when nearly every internet quitting site repeatedly echoes the authors' *Figure 3* efficacy suggestion that they are substantially more likely to fail. Although formal study of the keys to successful abrupt cessation has been neglected, practitioners would be wise to spend a few minutes exploring sites devoted exclusively to cold-turkey education, counselling and/or support.

What is the most critical lesson about abrupt cessation physicians can share? I submit that it flows from lapse/relapse studies, that 'the high rate of return to regular smoking (88%) once a cigarette is tasted suggests that the distinction between an initial lapse and full relapse may be unnecessary.'[4] And let's not forget that at least 10% of smokers are consistently identified as non-dependent chippers.[5]

Patients who smoke need to understand that recovery from nicotine dependence is all or nothing, that one puff will be too many, while thousands are never enough. They need to know that while most people who attempt cheating walk away feeling as if they have gotten away with it, just one puff and up to 50% of a4b2-type nicotinic receptors become occupied by nicotine.[6] And it won't be long before the lapsed patient who has lapsed finds their brain wanting, conspiring to obtain or even beg for more.

As for the tease of e-cigarettes, vaping and cleaner delivery, remind them that being free is vastly more doable and far more wonderful than their wanting for that next fix will suggest. Ask them why they would devote weeks or months towards adjusting to a new form of nicotine delivery when they could become 100% nicotine-clean and move beyond peak withdrawal within 72 hours. Just 1 hour and challenge at a time, yes they can!

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Competing interests: Pro bono director of WhyQuit, an abrupt nicotine cessation website, and author of *Freedom from Nicotine – The Journey Home*.

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Reply

Dear Editor

We thank Dr Polito for his response to our article. We do not believe that offering help to people who smoke when they present in general practice, or other clinical settings, in any way undermines those smokers who prefer to try to quit without assistance from a health professional. It is also important to note that population surveys, such as the study by Doran et al,[1] inevitably have risks of selection bias that may lead to underestimation of the effectiveness of smoking cessation treatment.[2–5] Clinical trials remain the most reliable measure of effectiveness and have been conducted in a range of settings with a variety of populations.

We agree with Dr Polito that nicotine is a highly addictive drug and given the fact that dependence can be rapidly re-established after further exposure, the not-a-puff rule makes good sense and indeed we recommend this approach in our article.

The issue of whether e-cigarettes have a possible role in harm reduction for people who are unable to stop using nicotine is quite a separate one and a question that needs further research.

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Sentinel lymph node biopsy

Dear Editor

In their viewpoint article concerning sentinel node biopsy (SNB) in melanoma management[1] (*AFP*, July 2014), Dixon et al appear to overlook the two main conclusions of the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I):

- 'Biopsy-based staging of intermediate-thickness or thick primary melanomas … identifies patients with nodal metastases who may benefit from immediate complete lymphadenectomy.'
- 'Biopsy-based management prolongs … melanoma-specific survival for patients with nodal metastases from intermediate-thickness melanomas.'[2]

The authors acknowledge that SNB is a diagnostic procedure but fail to realise that diagnostic procedures only have prognostic and therapeutic value in patients in whom the pursued abnormality is indeed found, eg a lymph node biopsy for suspected lymphoma will only lead to treatment if the disease is found, and only then can an impact on survival be expected. This is also true for SNB. Appropriate subsequent therapy can only improve survival in patients with an involved sentinel node. Therefore, the most important outcome of MSLT-I concerns the patients with intermediate thickness melanomas in whom lymph node metastasis is found. In this prespecified target population, management determined by SNB substantially increases the survival rate compared to those who did not undergo SNB staging and developed palpable nodal disease later (10-year survival 62% vs 41%). Such an improvement in survival is exceptional in oncology and cannot be ignored.

The MSLT-I final report also shows that occult metastases in lymph nodes progress to clinically relevant disease over time. SNB-positive patients have a 12–20% risk of having more involved nodes. Whether a completion node dissection is required in all these patients is not known. This is the subject of another trial, MSLT-II, but it appears prudent to perform completion lymph node dissection until the outcome of this study is known.

We conclude that there is now convincing evidence to recommend SNB in patients with a clinically localised melanoma of intermediate Breslow thickness and to consider the procedure in patients with a thinner or thicker lesion. The American Society of Clinical Oncology and the Society of Surgical Oncology, the most respected medical and surgical oncology groups in the world, made the same recommendation in their joint, evidence-based guideline.[3]

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Reply

Dear Editor

Thank you for the opportunity to respond to the suggestion that a sub analysis within the multicentre selective lymphadenectomy trial (MSLT-I) data[1,2] justifies continued usage of sentinel lymph node biopsy (SLNB) as a treatment.

Like any randomised controlled trial (RCT) the important data is on an intention to treat (ITT) basis. The ITT data is clear. There was no 10-year melanoma specific survival benefit for intervention patients (77%), versus observation (76%). Even intermediate thickness melanoma patients failed to gain a survival benefit from SLNB and completion lymphadenectomy (CL). This is a negative study. Examination of sub analyses is always fraught with danger. There is naturally a wish to try and salvage something of clinical relevance from these seminal studies.

So, what of these subanalyses? We agree that SLNB gives patients added prognostic information; coming with the risks of surgery.[3] More melanoma lymph nodal involvement (MNI) occurred in the intervention group (19.9%), versus the observation group (17.4%). The intervention group MNI comprises SLNB positive patients (15.9%) and patients that were biopsy negative but later developed nodal disease (4%). This demonstrates that the SLNB test is not perfect. This discrepancy explains many other curious subanalyses

We are asked to compare all in intervention patients with MNI (this 19.9%) with observation patients that developed MNI later. There is a suggested survival advantage in finding MNI early (62%), versus waiting for MNI to become clinically apparent (41%). But this is an extracted data set from an RCT showing no ITT survival benefit. Therefore it is not surprising that those in the intervention group that never had MNI still had a high ten year mortality rate of 17%. This compares *unfavourably* with 10-year mortality in the observation group that never developed MNI (12.5%!).

If we are to believe doing an SLNB and finding an early positive node saves lives, then we would have to believe that having negative SLNB test is killing other patients. Of course, neither is the case. It is just another example of the serious pitfalls in straying from an ITT analysis.

The current MSLT-II trial will provide further useful data. In this trial patients who have a positive SLNB are randomised to either CL or observation. We encourage patients who have a positive SLNB test to consider enrolment in this trial.

We disagree that SLNB positive patients should be invited to proceed to CL outside of the MSLT 2 clinical trial. Indeed to encourage patients to have this further major procedure with a 37% complication rate[3] with no apparent survival benefit raises ethical and moral questions. MSLT-1 has taught us that we need to avoid a presumption of surgical benefit. Let us not repeat history.

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Sports-related concussion

Dear Editor

The authors of the article on sprots-related concussion (*AFP* March 2014)[1] state their conflicts of interest appropriately at the end of the article, which is good, but it still seems that overall it is biased in favour of using screening neuropsychiatric tests (SCAT3, ImPACT, King-Devick) for a purpose they were not developed for (ie return to competition). It is not that these tests are not helpful, just that this application for them has not been truly validated.

The tests were designed to have a high sensitivity and while we would all accept a false-positive rate in the acute phase of injury, to remove a potentially at-risk player from the field, the reduced specificity means we might be keeping players from re-engaging when in fact concussion may not be the cause of their off-baseline test result.

Additionally, while the graded return to play makes sense and would be what most practitioners do in the absence of better information, it is worth being aware that the authors do not mention the trial that showed a worse outcome with respect to the incidence of subsequent concussive events in football players kept from competition until complete resolution of their features, compared with players who returned prior to complete symptom resolution;[2] admittedly, however, the symptom-free players managed to return to play 2–3 days earlier than those with persistent symptoms.

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Reply

Dear Editor

Dr MacPartlin's letter raises important issues regarding recovery following concussion and decisions regarding safe return to play.

Concussion is considered to be a functional rather structural injury.[1] The clinical features typically come on rapidly but resolve spontaneously over a sequential course.[1] The majority of individuals recover uneventfully following concussion; however, the time course of recovery is variable and complications can occur.[1] While risk factors for complications remain unclear, the current consensus is that premature return to play following concussion (ie before the athlete has recovered clinically) increases the risk of both short- and long-term complications.[1]

Few studies, however, have assessed the outcome of return-to-play decisions. As mentioned in the letter, a study by McCrae et al compared cases where a symptom-free period was either observed or not observed before return to play.[2] The results showed that there were no significant differences in clinical outcome with respect to symptom recovery or performance on neuropsychological and balance testing between the groups. Further, they found a higher rate of repeat concussion in the group that was managed by waiting for symptoms to resolve before return to play, although the overall rate of recurrence was low and those with a repeat concussion recovered relatively quickly.

In a large scale prospective study performed in Australian football, our group assessed the outcome of return-to-play strategies that mirrored current recommendations (ie players were symptom-free and had returned to baseline on simple tests of cognitive function before being returned to competition).[3] We found that players were able to return to sport safely, with no detrimental effect on performance and no increased risk of concussion or other injury on return to play.[3] No studies to date, however, have assessed the impact of return-to-play strategies on risks of long-term complications.

One of the key difficulties for clinicians is that there is no single objective or direct marker of recovery following concussion. Consequently, it is recommended that combined clinical measures be used to estimate recovery and make decisions regarding return to play.

While symptoms are important, it is recognised that many of the symptoms are not specific for concussion. Moreover, they are subjective and are not reliably reported by athletes. Conversely, symptoms have been observed to resolve independently to (and often before) recovery of cognitive function.[4,5]

Balance testing has been shown to useful in the early stages following concussion. Deficits seem to be most pronounced within 24 hours of injury and tend to resolve within 5–7 days post-injury.[6]

Screening neuropsychological tests add a further degree of objectivity to the post-concussion assessment. The tests allow detection of deficits in brain function that are commonly observed following concussion (eg reaction time, memory, information processing, etc). They are not, however, without their limitations.[7] Simple pencil and paper tests and computerised screening test batteries have a role in the assessment of recovery following concussion but these tests should never be used in isolation. Nor is there sufficient evidence currently to recommend widespread baseline testing.

The authors also mention the King-Devick test as an example of a neuropsychological test. It must also be pointed out, that the King-Devick test was developed as a test for assessing saccadic eye movements, particularly in children with reading dysfunction. While its utility in sports concussion is now being assessed, it is neither a stand-alone neuropsychological test, nor a replacement for clinical assessment in sports concussion.

Overall, it must be remembered that none of the clinical measures in themselves should be used as the sole basis for management decisions (to either return to or withhold from activity). Rather, they should be used to help guide clinical decision-making. When making return-to-play decisions, the medical practitioner must always ensure that the primary consideration is the player's welfare. As such, the Zurich Consensus Statement errs on the side of caution and

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recommends no return to play while symptomatic. However, as we state in our paper, when an athlete demonstrates clinical complexities, such as prolonged symptoms, then more formal assessment is required.

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What is the optimal level of vitamin D?

Dear Editor

The paper by Robyn Lucas and Rachel Neale addresses the question: What is the optimal level of vitamin D? [1] Unfortunately, they seem to have chosen papers from the literature to support their idea that 50 nmol/L is adequate, ignoring other papers that support higher levels. The purpose of my letter is to point out some of the problems with the papers they cited and present some of the findings in papers they overlooked.

The Institute of Medicine committee based its recommendations on vitamin D randomised controlled trials (RCTs) published by the end of 2010, ignoring observational studies except to point out that some showed evidence of adverse effects at higher 25-hydroxyvitamin D [25(OH)D] levels. Lucas and Neale also misinterpreted one key paper on bone condition with respect to 25(OH)D levels.[2] The authors of that paper clearly stated that 75 nmol/L, not 50 nmol/L, was the cut-off point for healthy bones. As for RCTs, vitamin D RCTs have largely been poorly designed and conducted as they have been designed on the pharmaceutical drug model: that is, that the agent used in the study is the only source of the compound and that there is a linear dose-response relationship between intake and effect. Neither is satisfied for vitamin D due to the abundant other sources. The proper way to design vitamin D RCTs has been outlined in a pair of recent papers.[3,4] Thus, observational studies provide better evidence for now than RCTs regarding the optimal 25(OH)D levels.

As for the relationship between 25(OH)D level and parathyroid hormone (PHT), a paper based on over 310,000 measurements found that PTH decreased monotonically as 25(OH)D level increased out to 187 nmol/L.[5] The decrease of PTH for 25(OH)D increasing from 50 to 187 nmol/L was 35%.

As to possible risks for higher 25(OH)D levels, two things should be kept in mind. One is that for health outcomes, for which there are many studies, the meta-analysis of all available studies should be considered, not single studies. For prostate cancer, the result of meta-analyses is that there is no general relationship between low and high 25(OH)D levels and risk of prostate cancer,[6] but there is increased risk of aggressive prostate cancer at low 25(OH)D levels.[7] For all-cause mortality rate, while there may be a slight upturn at higher 25(OH)D levels based on studies to date, it is not significant.[8] The second thing is that some of the increased risk of adverse health outcomes could be due to enrolling people in the cohort studies who were recently told to take more vitamin D due to a health condition such as osteoporosis. This effect was demonstrated in a pair of studies on frailty:[9,10] for elderly men, there was an inverse correlation of frailty status with respect to 25(OH)D level several years after enrolling in the study,[9] whereas for elderly women, there was a U-shaped relationship with higher frailty status associated with both low and high 25(OH)D levels.[10] Elderly women are much more likely to be advised to take vitamin D than elderly men in the United States.

Another concern regarding observational studies is that 25(OH)D levels change with time. Thus, the longer the time since blood draw, the less likely that the level measured corresponds to the average value. This effect has been observed for breast and colorectal cancer[6] and all-cause mortality rate.[11] Thus, the statement 'the strength of the evidence for an association between 25(OH)D levels and breast cancer decreased as the quality of the study design increased' is incorrect. What was reported in the referenced study was that the odds ratio for highest quantile versus lowest quantile 25(OH)D level was 0.86 (95% confidence interval, 0.75–1.00) for nested case-control and retrospective studies, 0.35 (0.24–0.52) for population-based case-control studies, and 0.08 (0.02–0.33) for hospital-based case-control studies.[12] When it is also considered that breast cancer can develop very rapidly, as evidenced by the fact that breast cancer diagnoses peak in spring and fall,[13] and that a meta-analysis of breast cancer survival with respect to 25(OH)D levels at time of diagnosis found a hazard ratio of 0.50 (0.45–0.58),[14] the designation of quality of study for 25(OH)D levels is actually the inverse of what is commonly accepted.

On the basis of 25(OH)D level–health outcome relationship, I estimated that if population mean 25(OH)D levels were increased from 54 to 110 nmol/L, all-cause mortality rates would decrease by 7–17%, depending on the continent, and life expectancies would increase by 2 years.[15] The bases for the calculations were subsequently supported by the 25(OH)D level–outcome relations from meta-analyses for cardiovascular disease[16] and diabetes mellitus.[17]

As for optimal 25(OH)D levels, many reviews by individuals and groups have recommended 75 nmol/L or higher, on the basis of the best evidence available at the time.[18–25] Given the concern about the risk of skin cancer and melanoma in Australia, vitamin D supplements might be preferred to solar ultraviolet-B irradiance. However, it is noted that there is considerable variability in changes in 25(OH)D level for any given oral vitamin D intake.[26] Thus, measurement of 25(OH)D level before and after commencing a vitamin D supplementation program might be in order.

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Reply

Dear Editor

We thank Dr Grant for his comments on our manuscript and agree that different interpretations of the existing data are possible. Below we address some of the issues that Dr Grant has raised.

Priemel and colleagues interpreted the results of their study of 25(OH)D and bone morphology in autopsy specimens to imply that a 25(OH)D level of at least 75 nmol/L is needed to optimise bone health.[1] However, we contend that the results did not provide sufficient data to support such a concrete recommendation. Firstly, a very low proportion of people (<1%) with 25(OH)D concentration between 50 and 74 nmol/L had evidence of mineralisation defects, compared with none in the group of people with 25(OH)D >75 nmol/L. In addition to the very small difference in this proportion, the total number of people with 25(OH)D >50 nmol/L was low. There was no statistical analysis to confirm that the differences in the proportion of people with mineral defects in the two groups with 25(OH)D over 50 nmol/L was not due to chance. Importantly, the vast majority of people with a level below 50 (or even 25 nmol/L) showed no evidence of bone mineralisation defects, so this metric cannot be used to define a 25(OH)D cut-off.

The threshold at which parathyroid hormone (PTH) is minimised is not clear, with studies finding a range of different thresholds and others a continuously decreasing risk.[2] The study to which Dr Grant referred did indeed show that there was no 25(OH)D threshold beyond which levels of PTH stabilised.[3] The implication is that indefinitely increasing 25(OH)D to the limit of toxicity will be beneficial, which is almost certainly inadvisable given the potential risks at higher levels (see below). Interestingly, a surprising proportion of people (49%) had normal PTH despite frank vitamin D deficiency. Thus, use of PTH in isolation to determine a 25(OH)D cut-point is not appropriate.

Regarding the U-shaped curves we highlighted, we agree that the evidence is inconsistent. This is almost certainly due to the nature of epidemiology – differences in the population, timing of measurement, measurement of both 25(OH)D and confounding variables, data analysis and interpretation could all lead to different results. Meta-analyses can solve this problem to some extent, but a number of studies showing the increased risk at higher levels have been published since the relevant meta-analysis, and data are constantly changing. For example, manuscripts have very recently been published which suggest a U-shaped curve for prostate cancer (minimum risk at a 25(OH)D level of approximately 50–75 nmol/L[4] and fragility fractures (minimum risk at a 25(OH)D level of 60–72 nmol/L).[5] With respect to total mortality, a meta-analysis did confirm that there appears to be a turning point.[6] While we agree that any increased risk of disease at higher levels of 25(OH)D is not well established, we feel that there is sufficient evidence to warrant sounding a note of caution.

Different types of observational studies, and indeed trials, have advantages and disadvantages. However, we do not believe that studies of vitamin D should be exceptions to the commonly accepted wisdom that cohort studies provide more reliable data in most circumstances than case-control studies. In case-control studies, when blood is collected after diagnosis of disease, any association is likely to be due to reverse causality. Using breast cancer as an example, if patients have been sitting in waiting rooms, consulting with multiple health professionals, and undergoing surgery or other treatment, their 25(OH)D levels will almost certainly decline due to reduced sun exposure and possibly due to the effects of the disease or treatment. Studies have shown seasonally adjusted 25(OH)D levels to be stable over time, suggesting that baseline levels in cohort studies are a good marker of longer-term exposures.[7]

There is no doubt that frank vitamin D deficiency is a health risk, but beyond that it is currently unclear where 25(OH)D cut-off should lie. At this point we concur with the Institute of Medicine and Osteoporosis Australia that a level of 50 nmol/L is probably sufficient for most people. If this threshold is used, most Australians do not have low 25(OH)D levels (23% of the Australian population, across all seasons, in the recent Australian Health Survey). Therefore, routine population screening, which is currently costing upwards of $140 million per annum, is not warranted and general practitioners should follow published guidelines to determine whom to test.

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Eye care in the elderly

Dear Editor

We commend Dr Green and associates for highlighting the importance of early detection for ocular and visual conditions among elderly Australians, the benefits of co-management and the barriers to timely access to eye care among the elderly (*AFP*, July 2014).1

The role of optometry as a critical entry point into the eye care continuum for socially disadvantaged elderly Australians should not be overlooked. As Australia's primary eye care providers, optometrists provide approximately 75% of all primary eye care consultations.[2,3]

In addition to correcting refractive error, optometrists enjoy a broad scope of practice that spans from detecting ocular disease associated with ageing, including cataract, diabetic retinopathy, macular degeneration and glaucoma, through to managing common acute eye complaints with topical eye drops (for those optometrists who are therapeutically endorsed). Today, all optometry graduates commence practice with this prescribing authorisation.

As highlighted by Green et al,[1] many elderly Australians experience varying degrees of social isolation as a result of frailty, living alone or in a residential facility, creating a barrier to accessing mainstream eye care services. Indeed, isolation can itself be associated with vision problems. Many optometrists have the capability to provide comprehensive eye examinations to elderly patients in domiciliary settings and conduct low vision assessments.

Effective collaborative relationships between optometrists, ophthalmologists and general practitioners are essential to improve eye health outcomes for socially disadvantaged elderly patients.

Despite the need for accessible primary eye care among elderly Australians, domiciliary optometric service provision remains suboptimal with less than 5% of Australia's 4500 practising optometrists providing regular eye care in a residential aged care facility and less than 2% in the home.[1] To increase the provision of primary eye care for patients who are unable to access mainstream optometry practice, better incentives and improved Medicare coverage for such services are needed to make domiciliary eye care viable for optometrists. In many instances, greater recognition among aged care providers of the need to facilitate optometry service provision for their clients is also needed.

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Letters to the Editor

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