PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

ABSTRACTED MONTHLY FROM THE JOURNALS

A Free Public-service Publication

FEBRUARY 2014

JAMA, NEJM, BMJ, LANCET
JAMA INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA

www.practicalpointers.org A free public-service publication. To request monthly issues go to Rjames6556@aol.com

26th YEAR OF PUBLICATION

Practical Pointers is published every month on the internet as a public service.

The complete content of all issues for the past 10 years can be accessed at

www.practicalpointers.org

It is also available on a more timely basis by e-mail attachment. It contains no advertising. It is completely without bias. There is never any charge.

Requests for "subscription" to rjames6556@aol.com

I hope you will find *Practical Pointers* interesting and helpful.

Richard T. James Jr. M.D.

Editor/Publisher.

The editor thanks

Lois M, James for proof reading

Matthew Ramirez for internet application

2-1 2014 EVIDENCE-BASED GUIDELINES FOR THE MANAGEMENT OF HIGH BLOOD PRESSURE IN ADULTS: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC-8)

Clinical guidelines are at the intersection between research evidence and clinical action that can improve patient outcomes.

The panel members, appointed to the JNC-8 by the NHLBI, used rigorous evidence-based methods for BP treatment based on a systematic review to meet user needs, especially the needs of primary care.

The guideline focuses on the panel's 3 highest-ranked questions related to high BP management:

1) In adult hypertension, does initiating anti-hypertension pharmacologic therapy at specific BP thresholds improve health outcomes?

2) In adult hypertension, does treatment with anti-hypertension pharmacological therapy to a specific BP goal lead to improvements in health outcomes?

3) In adult hypertension, do various anti-hypertension drugs or drug classes differ in comparative benefits and harms on specific health outcomes.

The Evidence Review:

Focused on adults age 18 and older with hypertension. Studies with sample sizes less than100, and follow-up of less than 1 year were excluded.

Included studies focused on important clinical outcomes (eg, mortality cardiovascular disease, myocardial infarction, heart failure, end stage renal disease and others). Only randomized, controlled trials (RCTs) were included.

There are major differences between this report (JNC-8) amd the previous report (JNC-7).

Recommendations: (There are 9)

1) In the general population aged 60 and older, initiate drug treatment to lower systolic of 150 and over, or diastolic of 90 and over. Treat to a goal of lower than 150/90. (Strong recommendation –Grade A)

If drug treatment results in lower systolic BP (eg, < 140) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert opinion- Grade E)

There is moderate-to-high quality evidence from RCTs that, in the general population age 60 and older, treating high BP to a goal lower than 150 reduces stroke, heart failure, and coronary heart disease.

There is low-quality evidence that setting a goal lower than 140 in this age group provides no additional benefit compared with a higher goal of 140 to 149.

2) In the general population younger than age 60, initiate drug treatment in patients with diastolic BP 90 and above and treat to a goal lower than 90.

For ages through 30-59, (Strong recommendation—Grade A.

For ages 18-29 (Expert opinion—Grade E)

Treatment lowers cerebrovascular events, heart failure, and overall mortality.

There is no benefit in treating to a goal of 80 or lower or 85 or lower compared with 90 or lower.

In adults younger than 30, there are no good quality RCTs that assessed the benefits of treating elevated diastolic BP on health outcomes.

In the panel's opinion, adults younger than 30, diastolic goals should be the same as adults age 30-59.

3) In the general population under age 60, initiate drug treatment in patients with systolic equal to or over 140 to a goal of less than 140. (Expert opinion)

4) In the population age 18 and over with chronic kidney disease (CKD) with systolic equal to or over 140 or diastolic equal to 90 and over treat to a goal of less than 140/90 (Expert opinion)

Based on the RCTs reviewed by the panel, this recommendation applies to individuals under age 70 with an estimated GFR of less than 60 mL/min/173/m^2, and in patients at any age with albunimuria greater than 30 mg/gram of creatinine at any level of GFR.

No trial showed that treatment to a lower goal (eg, less than 130/80) significantly lowered kidney or cardiovascular disease endpoints compared with a goal of lower that 140/90.

5) In the population aged 18 and over with diabetes, initiate drug treatment in patients with BP equal to or higher than 140/90 to reduce BP to under 140/90. (Expert opinion)

The panel recognizes that a systolic lower than 130 is commonly recommended for adults with diabetes and hypertension. However, this goal is not supported by any RCTs. There is not sufficient evidence to recommend lowering diastolic below 80.

6) In the general non-black community, including those with diabetes, initial drug treatment should include a thiazide-like diuretic, calcium channel blocker, (CCB). angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate strength recommendation)

Each of the 4 classes of drug yielded comparable effects on all-cause mortality, and cardiovascular, cerebrovascular, and kidney outcomes. However, for heart failure, initial treatment with a thiazide was more effective.

However, the panel also acknowledged that the evidence supports BP control, rather than the specific agent used to achieve the BP goal.

The panel did not recommend beta-blockers for the initial treatment of hypertension because in only 1 study beta-blocker use resulted in higher rate of the primary composite outcome of cardiovascular death, myocardial infarction or stroke compared with ARB, a finding largely driven by increase in stroke.

Alpha-blockers were not recommended as first-line therapy because in one study initial treatment resulted in worse cerebrovascular, heart failure, and combined cardiovascular outcomes than initial treatment with a diuretic.

There were no RCTs of good quality comparing the following drug classes to the 4 recommended classes: dual alpha- and beta-blocking agents (eg, carvedilol), vasodilating beta-blocker (eg, nebivol), central alpha-adrenergic agonists (eg, clonidine), direct vasodilators (eg, hydralazine), aldosterone neuronal depleting agents (eg, reserpine). and loop diuretics (eg, furosemide). Therefore these drug classes are not recommended as first-line therapy.

The following important points should be noted:

1. Many people will require treatment with more than 1 drug to achieve control. While this recommendation applies only to the choice of an initial drug, the panel suggests that any of the 4 classes would be good choices as add-on agents.

2. This recommendation is specific for thiazide-type diuretics. It does not include loop or potassium-sparing diuretics.

3. It is important that medications be dosed adequately to achieve results similar to those seen in RCTs.

4. RCTs that were limited to specific non-hypertensive populations, such as those with coronary artery disease or heart failure, were not reviewed for this recommendation.

7) In the general black population, including those with diabetes, initial antihypertension treatment should include a thiazide-type diuretic, or a CCB. (Moderate recommendation) For blacks with diabetes. (Weak recommendation)

8) In the population age 18 and over with chronic kidney disease, initial (or add-on) treatment should include an ACEI or ARB to improve kidney outcomes. This applies to CKD patients with hypertension regardless of the diabetes state. (Moderate recommendation)

This recommendation is specifically directed at those with CKD and hypertension, and address the potential benefit of specific drugs on kidney outcomes.

Both ACEI and ARB have been shown to have similar effects on kidney outcomes.

ACEI and ARB will commonly increase serum creatinine and potassium in patients with kidney dysfunction. This requires monitoring.

9) The main objective of hypertension treatment is to attain and maintain goal BP. If the goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide, CCB, ACEI, of ARB). The clinician should continue to assess BP and adjust treatment until goal BP is reached. If the goal cannot be reached with 2 drugs, add a third from the list. Do not use an ACEI and an ARB together. (Expert opinion)

This recommendation also applies to diabetics.

Each strategy is an acceptable drug treatment strategy that can be tailored based on individual circumstances, clinician and patient preferences, and tolerability. With each strategy, clinicians should regularly assess BP, encourage evidence-based lifestyles, encourage adherence, and adjust treatment until goal BP is attained and maintained. In specific situations, an anti-hypertension drug may be replaced with another if the first drug is not effective or there are adverse effects.

To sum up the present guideline

Population	Goal	Initial dug treatment options
General ≥60	<150/90	Non-black; thiazide, ACEI, ARB, CCB
		Black: thiazide or CCB
General < 60	<140/90	Thiazide, ACEI, ARB, or CCB
Diabetes	<140/90	Thiazide, ACEI, ARB, or CCB
CKD	<140/90	ACEI or ARB

Conclusion:

It is important to note that this evidence-based guideline has not redefined high BP, and the panel believes that 140/90 remains reasonable.

The relationship between naturally occurring BP and risk is linear down to very low BP, but the benefit of treating to these low levels with drugs is not established.

For all patients with hypertension, the potential benefits of a healthy diet, weight control, and regular exercise cannot be overemphasized. Lifestyle treatments have the potential to improve BP control, and reduce medication needs.

These recommendations are not a substitute for clinical judgment. Decisions about care must be carefully considered and incorporate the clinical characteristics and circumstances of each individual.

JAMA February 5, 2014;311:507-520 First author Paul A James, University of Iowa, Iowa City.
doi.10.1001/jama.2013.284427 jama.2014;(5):507-520
An algorithm on page 516 condenses these recommendation.

We appreciate the effort and time the panel spent to review the massive data and condense it into simple recommendations.

Guidelines come and guidelines go. This is a work in progress. Updates will eventually follow. Of the 9 recommendations, 5 are based on expert opinion.

The panel made no recommendations about how the BP should be determined. It would be easy if BP readings were constant during the day and night, and according to stress and physical activity. I believe the best we can do is to acquire a reliable battery operated machine and average readings over 24 hours. The accuracy of the machine should be correlated with the office machine.

Adverse effects of antihypertension drugs (eg, falls) may be more common in the elderly.

Mammography In Women Age 40-59 Did Not Reduce Mortality From BC Beyond That Of Physical Examination Or Usual Care

2-2 TWENTY FIVE YEAR FOLLOW-UP FOR BREAST CANCER INCIDENCE AND MORTALITY: The Canadian National Breast Cancer Screening Study, Randomized Screening Trial.

To what extent does mammography screening reduce mortality from breast cancer (BC)?

In this long-term Canadian study, 89 835 women age 40-59 were randomly assigned (from 1980-85) to mammography or to a control arm (no mammography).

Women age 40-49:

Randomly assigned to:

1) Mammography arm—5 annual mammography screenings plus 5 annual physical breast examinations.
2) Control arm—no mammography and a single breast physical examination followed by usual care in the community.

Women age 50-59:

1) Mammography arm - 5 annual mammography screens plus 5 annual physical breast examinations.
2) Control arm (no mammography). All received 5 annual breast physical examinations.

Primary outcome = mortality from BC 5 years after screening, and at the completion of follow-up at 25 years.

RESULTS

1. During the 5-year screening period, 666 invasive BCs were diagnosed in the mammography group, and 524 in control group.
2. After 15 years of follow-up, an excess of 106 cancers was observed in the mammography arm, attributed to over diagnosis. This represents 22% of all screened invasive cancers. Therefore, for every 424 women screened by mammography, one BC was overdiagnosed.
3. 180 women in the mammography group and 171 in the control group died of BC.
4. The overall hazard ratio for death from BC during the 5-year screening period associated with mammography vs control was 1.05.
5. The cumulative rate of BC diagnosis during the entire study was similar between women in the mammography group and control group (Hazard ratio = 0.99)

6. The findings for women age 40-49 and 50-59 were almost identical.

7. Deaths due to BC to 31 December 2005 by study arm and year of diagnosis:

	Mammography (n = 44 925)	Control (n = 44 91-)
Death from BC detected in years 1-5	180	171
BC deaths per 100 000 women	40	38
Deaths from BC detected in years 6-25	288	321
BC deaths per 100 000 women	66.3	71.4
Total BC deaths (all years)	500	505
BC deaths per 100 000 women	108	110

(In a few patients the year of death could not be determined.)

The lack of any impact of mammography screening on mortality from BC in this study cannot be explained by bias, confounding, lack of statistical power, or poor quality of mammography.

CONCLUSION

Annual mammography in women age 40-59 did not reduce mortality from BC beyond that of physical examination or usual care when adjuvant therapy for BC was freely available.

Women with non-palpable BC detected by mammography experience long-term survival that is superior to that of women with palpable BC. This trial found that annual mammography screening detected a significant number of small non-palpable BCs, but had no impact on BC morality.

The rationale for screening by mammography should be urgently reassessed.

BMJ February 15, 2014; 348:12 BMJ2914;248:g366 doiL10.1136/bmj.g366

First author Anthony B Miller, University of Toronto, Canada

Study supported by the Canadian Breast Cancer Research Alliance and others.Central coordinating centre—The University of Toronto.

What about women over age 60?

This is bound to produce dissent. There will be continued disagreement. Meanwhile, let the informed patient decide.

The control group varied from usual patients who do not receive mammography.

Patients in the community do not receive expert physical examinations for BC. They do not perform periodic self-examinations of the breasts as in the trial control group.

==========

Long-Term Follow-Up Does Not Support Screening Women Under 60

2-3 TOO MUCH MAMMOGRAPHY: Editorial

(This editorial comments and expands on the preceding trial.)

Before widely implemented, mammography screening was tested in randomized trials in 1960s-1980s. Meta-analyses of trials showed a relative reduction in deaths from BC of between 15% and 25% among women age 50-60. Only the Canadian National Breast Screening Study showed no reduction in cancer mortality.

The study described in the preceding article is a 25-year follow-up of the earlier Canadian study.

The major strengths of this study include its randomized design, intense intervention with 5 annual mammography screenings, high compliance, and complete, long-term follow-up.

The lack of mortality benefit is biologically plausible because the mean tumor size was 19 mm in the screened group, and 21 mm in the control group. The 2 mm difference represents a minimal proportion of the entire clinical course for breast tumors.

The rate of overdiagnosis did not include ductal carcinoma in situ and the trial provided no data on women over age 60.

This study is the only trial to enroll participants in the modern era of routine adjuvant systematic treatment of BC, and in women who were educated in physical breast examination as advocated today.

Other studies also indicate that improved treatment, rather than screening, is the reason for the recent decline in BP mortality.

The editorialist points out that screening for prostate cancer with prostate-specific antigen and mammography screening have much in common: high rates on overdiagnosis and little effect on mortality. (PC screening by PSA is not encouraged in the UK.)

The aim of the UK National Screening Committee is to implement only programs that do more good than harm. Informed choice is the guiding principle of screening.

As time goes by we need more efficient mechanisms to reconsider priorities and recommendations for mammography screening and other medical interventions. This is not an easy task, because governments, research funders, scientists, and medical practitioners may have vested interests in continuing activities that are well established.

BMJ February 20;348:8 BMJ 2014;348:g1403

Editorial, first author by Mette Laager. University of Oslo, Norway.

A news article in this issue of BMJ (page 1) by Sophie Arie, notes that Switzerland is debating dismantling its breast cancer screening program because it leads to too many unnecessary interventions. While systematic screening for BC can save 1 -2 lives for every 1000 screened, it led to unnecessary investigations and treatment for about 100 women. Screening is not cost-effective.

The Swiss Cancer League said it was "astonished" at the report.

The new guidelines on high blood pressure and prevention of cardiovascular disease with statin drugs, and now, this report on efficacy of mammography have caused heated debate and differing opinions. How should the primary care clinician respond?

Dr Harlan M Krumholz responds in JAMA April 9. 2014 pages 1403-05. I quote one paragraph:

"Emerging from these documents and others is the sense that guidelines should inform, not dictate, guide but not force, and support but not restrict. Guidelines can provide options and recommendations for those seeking to improve the quantity and quality of their lives. They can indicate strategies that are, in the opinion of experts, outside of evidence and unworthy of pursuit. They can highlight points of uncertainty. But they should not reduce physicians to automatons and patients to passive recipients of guideline dictums. The idea of there being a "right answer" is what has entangled these guidelines in controversy, and the evolution away from this approach will have marked implications for quality measurement and board examinations. If the guidelines focus on providing recommendations and promoting choice, then the debate changes. There will still be opinions about how to interpret the evidence, such as whether to recommend therapy based on risk, but it may feel different if the guideline is assumed to impose practice."

==========

The Medical Letter For Drugs And Therapeutics

2-44 NEW ORAL ANTICOAGULANTS FOR ACUTE VENOUS THROMBOEMBOLISM

Patients with acute VTE are often treated initially with parenteral anticoagulants such as unfractionated heparin, low molecular weight heparin, or fondaparinux. All are associated with similar rates of mortality, recurrent VTE, and major bleeding. For most patients, oral vitamin K antagonist (warfarin) is started on the same day as parenteral therapy and titrated to a mean INR of 2.0 to 3.0. After about 5 days, the parenteral anticoagulant is stopped and warfarin is continued as monotherapy, usually for 3 months.

New oral anticoagulants:

Dabigatran (Pradaxa), rivaroxaban (Xalto), apixaban (Eliquis) and edoxaban (not FDA approved) have been studied for treatment of VTE, but only riveroxaban is presently FDA approved for this indication. Unlike warfarin, these new drugs do not require INR monitoring and have no dietary restrictions, but they have shorter half-lives (increasing the risks associated with missed doses). There is no specific antidote to reverse the anticoagulant effect.

Only a small minority of patients in any clinical trial of a new oral anticoagulant for treatment of VTE were 75 years of age and older, had a creatinine clearance of less than 50 mL per minute, or had cancer.

Dabigatran (Pradaxa; Direct thrombin inhibitor)

A 6-month randomized, double-blind trial in 2539 patients compared dabigatran with warfarin for treatment of acute VTE. Twice-daily dabigatran was non-inferior to warfarin in preventing recurrent VTE or VTE-related death. Rates of major bleeding were the same in the 2 groups.

Rivaroxaban (Xalto; Factor Xa inhibitor)

(Is the only new anticoagulant drug presently approved for treatment of VTE.)

A randomized open-label study of 3449 patients compared rivaroxaban alone with low molecular weight heparin plus a vitamin K antagonist for treatment of acute VTE. Rivaroxaban was non-inferior to standard therapy in reducing the rate of recurrent VTE. The rate of major or clinically relevant non-major bleeding, the primary safety endpoint, was the same in both groups.

A second randomized open-label trial in 4832 patients with pulmonary embolism found rivaroxaban non-inferior to heparin plus a vitamin K antagonist in reducing the rate of recurrent VTE with similar rates of major or clinical relevant non-major bleeding.

Apixaban (Eliquis; factor Xa inhibitor)

A 6-month randomized, double-blind trial I5 395 patients compared apixaban alone to heparin plus warfarin for treatment of acute VTE. Twice daily apixaban was non-inferior in preventing recurrent VTE or VTE-related death. Major bleeding occurred less frequently with apixaban. (0.6% vs 1.8%)

(The reduction in major bleeding of 1 in 100 patients may be an advantage. Ed.)

Edoxaban (factor Xa inhibitor; not FDA approved)

In a randomized, double-blind trial of 8240 patients with acute VTE, edoxaban was non-inferior to warfarin in preventing acute VTE or VTE-related death.

Patients taking enoxaparin had a significantly lower rate of major or clinically-relevant non-major bleeding. (8.5% vs 10.3%)

Conclusion

The new oral anticoagulants dabigatran, rivaroxaban, and apixaban, and the investigational oral anticoagulant edoxaban all appear to be effective and safe for treatment of acute VTE, but data on older and sicker patients are limited.

They do not require INR monitoring and do not have dietary restrictions.

They have short half-lives that increase the risk of thrombosis with missed doses.

No specific antidote reverses their anticoagulant effect.

Oral anticoagulants for treatment of VTE

Drug	Mechanism	Cost $[a]
Warfarin (Generic)	Vitamin K antagonist	6
Dabigatran (Pradaxa)	Direct thrombin inhibitor	265
Rivaroxaban (Xarelto)	Direct factor Xa inhibitor	265
Apixaban (Eliquis)	Direct factor Xa inhibitor	265

(a Approximate wholesale cost for 30 days' treatment at the lowest dose.)

	Usual dose
Warfarin (Generic)	2-10 mg daily
Dabigatran (Pradaxa)	150 mg twice daily
Rivaroxaban (Xarelto)	15 mg twice daily for 3 weeks, then 20 mg once daily [b]
Apixaban (Eliquis)	10 mg twice daily for 7 days, then 5 mg twice daily

(b Once daily may be an advantage. Ed.)

JAMA February 19, 2014; 311: 731-32

JAMA is pairing with the Medical Letter on Drugs and Therapeutics to publish information on drugs

---

If the patient has been on warfarin for some time, and has been well controlled without bleeding, there is no reason to switch to a newer drug.

We do not know the efficacy and toxicity of the newer drugs in the elderly and in those with reduced kidney function.

Reassuring New Evidence For Smokers Who Want To Quit, Including Those With Mental Illness.

2-5 CHANGES IN MENTAL HEALTH AFTER SMOKING CESSATION: Systematic Review and Meta-analysis

In the general population and in the psychiatric populations does mental health change after smoking cessation compared with continuing to smoke?

Many smokers (with and without mental illness) want to quit, but continue to smoke. Some believe that smoking offers health benefits.

These investigators searched the literature up to 2012 for studies in adult smokers in the general population or from populations defined by the presence of other clinical characteristics. All studies (n = 26) reported data on people who had continued smoking and those who had quit during the study period.

Follow-up health scores were measured between 7 weeks and 9 years after baseline. Primary outcome was self-measures designed to assess anxiety, depression, positive affect, and psychological quality of life.

Anxiety, depression, mixed anxiety-depression, and stress significantly decreased between baseline and 9 years after baseline in quitters vs continuing smokers. Both psychological quality of life and positive affect significantly improved in quitters compared with continuing smokers. Some health care professionals are reluctant to approach cessation in people with poor mental health for fear that cessation might worsen their state. Studies do show that regular smokers experience depression, anxiety, and irritability in the few hours after not having smoked. Smokers assume that, because smoking abolishes these feelings, smoking improves their mental health. This is a misattribution. It is smoking that caused these problems.

BMJ February22, 2014; 348:12 First author Gemma Taylor, University of Birmingham, UK
BMJ2014;348:g1151

2-6 QUITTING SMOKING IS ASSOCIATED WITH LONG-TERM IMPROVEMENT IN MOOD: Editorial

Nicotine stimulates the release of many neurotransmitters in the CNS, including dopamine, norepinephrine, serotonin, endorphins, and GABA, which induce pleasure, arousal, mood modification, and a reduction in anxiety and tension.

Abrupt nicotine withdrawal is characterized by irritability, anxiety, difficulty concentrating, impatience, difficulty concentrating, depressed mood, impaired performance, increased appetite, experienced most acutely in the first 24 hours after quitting.

These symptoms typically resolve within 2 to 4 weeks after quitting.

Although depression is one of the less common symptoms of withdrawal, concerns that mood changes might persist or precipitate clinical depression can dissuade smokers from trying to quit and healthcare providers from intervening, especially among smokers with current or past mental illness.

The authors of the above study hypothesized that, individuals who quit would report improvements in mental health due to no longer experiencing the negative effects of smoking cessation induced by repeated states of acute nicotine withdrawal between cigarettes. They concluded that, compared with continuing to smoke, quitting was associated with improved positive mood states and quality of life, and significant reductions in depression, anxiety, and stress.

The effects, calculated from differences in standardized changes in symptom scores comparing quitters with non-quitters or relapsers, ranged from a quarter to about a half of a standard deviation. This is similar to the effects of antidepression drugs.

The pattern of findings was consistent and suggests, at the least, that quitting does no harm to long term mood.

There are several possible mechanisms for the benefit:

1) Quitting might improve mood, possibly through neuro-psychiatric recovery as the brain becomes unchained from the cycle of nicotine use and withdrawal.
2) Mood improvements might encourage quitting.
3) Other influences (eg, social support, exercise, or bupropion) could contribute to improvements in mood.

E-cigarettes—counterproductive?

Evidence to date indicates no benefit of e-cigs for quitting tobacco. There may be high rates of sustained dual use of e-cigs and tobacco and a lower likelihood of quitting tobacco among e-cig users. If chronic nicotine exposure via e-cig becomes the new norm, the sustained improvements in mood would probably be lost.

What about cessation drugs? (Varenicline and bupropion)

One to 2 weeks after the quitting date, declines in depression, irritability, anxiety and restlessness are greater in participants randomized to the active drug than to placebo. (But not to nicotine replacement therapy.)

Engaging smokers with concurrent mental illness in clinical trials has been one of the major successful shifts in tobacco control. Research supports that smokers with depression, schizophrenia, and post-traumatic stress disorder can quit without harming their chances of recovery.

The above study provides further reassurance that cessation will not worsen mood beyond the initial acute withdrawal period and suggests the possibility of mood improvement after quitting.

This is reassuring new evidence for smokers who want to quit, including those with mental illness.

BMJ February 22, 2014;348:8 Editorial by Judith J Prochaska, Stanford University, Stanford CA comments and expands on the preceding article. .
BMJ2014;348:g1562

Nicotine is a toxic substance. We still do not know all the adverse effect in inhaled pure nicotine. Studies have not been done.