Nicotine patches in pregnant smokers: randomised, placebo controlled, multicentre trial of efficacy

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Cite this as: *BMJ* 2014;348:g1622
doi: 10.1136/bmj.g1622

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g1622

bmj.com
Clinical review: Supporting smoking cessation (*BMJ* 2014;348:f7535)

STUDY QUESTION

Do 16 hour nicotine patches with dose individually adjusted to saliva cotinine level increase the quit rate in pregnancy and birth weight compared with placebo patches?

SUMMARY ANSWER

Despite individual dose adjustment, longer treatment duration, and a higher daily nicotine dose than in previous studies, nicotine patches did not increase the smoking cessation rate or birth weight compared with placebo patches.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Smoking during pregnancy increases the risk of adverse pregnancy and birth outcomes yet evidence about the efficacy of nicotine replacement therapies (NRT) in pregnant smokers is inconclusive for abstinence and birth weight. This trial found no benefit.

Design

A multicentre, randomised, double blind, placebo controlled trial with block randomisation and computer generated allocation.

Participants and setting

476 women aged more than 18 and between 12 and 20 weeks' gestation, who smoked at least five cigarettes daily and attended one of 23 maternity wards in France.

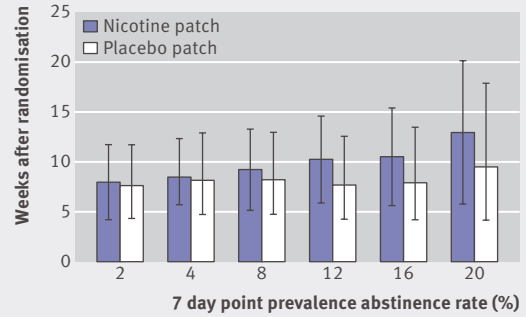
Primary outcomes

Complete abstinence (self report confirmed by carbon monoxide level in expired air ≤8 ppm) from quit date to delivery, and birth weight.

Main results and the role of chance

203 pregnant smokers were randomised to receive nicotine patches and 199 to receive placebo patches. Complete abstinence was achieved by 5.5% (n=11) of women in the nicotine group and 5.1% (n=10) in the placebo group (odds ratio 1.08, 95% confidence interval 0.45 to 2.60). The median time to the first cigarette smoked after the target quit day was 15 days in both groups (interquartile range 13-18 in nicotine group, 13-20 in placebo group). The point prevalence abstinence ranged from 8% to 12.5% in the nicotine group and 8% to 9.5% in the placebo group without statistically significant differences. The nicotine substitution rate did not differ from 100%, and the self reported median compliance rate was 85% (interquartile range 56-99%) in the nicotine group and 83% (56-95%) in the placebo group, assessed at 1016 visits. The mean birth weight was 3065 g (SE 44 g) in the nicotine group and 3015 g (SE 44 g) in the placebo group (P=0.41).

Seven day point prevalence abstinence rate (%) between week 2 and week 20 visits (last visit before delivery)



Bars indicate 95% confidence intervals

Harms

Diastolic blood pressure was significantly higher in the nicotine than in the placebo group. The frequency of serious adverse effects was similar, although more non-serious adverse reactions, mainly skin reactions, occurred in the nicotine group.

Bias, confounding, and other reasons for caution

It cannot be excluded with certainty that the study had insufficient power to show a significant difference in the rate of complete abstinence; however, the difference in smoking cessation was so low that 49 242 pregnant smokers would be needed in each group to provide a significant difference. Similarly, 1939 women should have been randomised to each group for the observed 50 g difference in birth weight to become statistically significant. Uncertainty exists about whether other forms of NRT or transdermal NRT started before or during the first weeks of pregnancy would yield superior results.

Generalisability to other populations

Participants were women seeking smoking cessation treatment in pregnancy, smoking at least five cigarettes daily; therefore, the results are difficult to generalise to other pregnant smokers. The trial's population was a highly tobacco dependent group. Generalisability of the results to a less dependent population of pregnant smokers should be done with caution.

Study funding/potential competing interests

Funded by the Ministry of Health, France (grant No MA05 00150). We have no competing interests.

Trial registration number

ClinicalTrials.gov NCT00507975.

References that anyone can edit: review of Wikipedia citations in peer reviewed health science literature

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Cite this as: *BMJ* 2014;348:g1585
doi: 10.1136/bmj.g1585

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g1585

STUDY QUESTION

What is the prevalence of Wikipedia citations in indexed health science journals, which journals publish articles with Wikipedia citations, and how is Wikipedia being cited?

SUMMARY ANSWER

Many publications cite information from Wikipedia, which is a tertiary source that can be edited by anyone, rather than an available permanent source.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The use of Wikipedia as a source of academic information has been debated since its origin, but it is increasingly cited in peer reviewed health science literature. Although a few instances exist that may warrant using Wikipedia as a reference, Wikipedia is often cited when permanent, evidence based sources are available.

Selection criteria for studies

This bibliometric analysis examined publications in the English language retrieved from the online databases Scopus and Web of Science that included citations to Wikipedia. We refined results by using Ulrich's database, selecting for citations from journals indexed in Medline, PubMed, or Embase. We collected impact factors from Thomson Reuters 2011 Journal Citation Reports for all journals included in the search. We thematically coded the resulting citations and calculated descriptive statistics.

Primary outcome(s)

We identified the number of papers citing Wikipedia and coded them according to the type of information that Wikipedia citations were used to support—for example, the results of original research, biographical information, and historical information.

Main results and the role of chance

We accessed a total of 1433 full text articles from 1008 journals indexed in Medline, PubMed, or Embase, with 2049 Wikipedia citations. The total number of Wikipedia citations has increased each year since 2004 except for between 2009 and 2010. The median impact factor of journals citing Wikipedia was 2.0 and has remained fairly consistent over time. Citations were not limited to journals with a low impact factor or no impact factor; our search found Wikipedia citations in many journals with a high impact factor. More than half of the citations were coded as definitions (n=648; 31.6%) or descriptions (n=482; 23.5%). We considered only 82 (4.0%) citations (from the categories Citations about Wikipedia and Wikipedia used in methods) to be appropriate uses of Wikipedia, as in these cases Wikipedia was the original source of information. Furthermore, we recovered 97 (4.8%) citations in which Wikipedia was cited in place of an original research study.

Bias, confounding, and other reasons for caution

Some citations may have been excluded from the search because of the search criteria used. However, the study used two comprehensive databases that probably captured most citations from journals with reaching influence as well as high impact factors.

Study funding/potential competing interests

This study was funded by the Children's Hospital of Eastern Ontario Department of Anesthesiology, University of Ottawa, and the Ottawa Hospital Department of Anesthesiology, University of Ottawa.

Five most frequent types of Wikipedia citations since 2001, categorised by code and impact factor

Coding strategy		Total citations—No (%)	Median (range) impact factor
Definition	A statement defining a word, phrase, item, or other symbol. This includes definitions of chemical formulas and equations that are not otherwise supported by original research references	648 (31.6)	1.9 (0.1-31.2)
Descriptive statement	Description of a process, system, or event. This differs from a definition, in that a process is explained without necessarily defining a term	482 (23.5)	1.9.4 (none*-31.2)
Historical	Description of a historical event. This can include the date, location, and a description of the events that took place	277 (13.5)	1.7 (0.1-36.3)
Statistics	Includes demographic and gross domestic product information (population size, including census information), geographical information, ratios, percentages, and averages	161 (7.9)	2.0 (none*-16.1)
Original research	Reporting results from a research study when on the Wikipedia page the original research is referenced but in the article the authors referenced Wikipedia, or the authors imply something like "research suggests that. . ." with no support other than Wikipedia	59 (2.9)	2.9 (0.7-8.8)
	Tools used, such as laws, formulas, or scales that could have been referenced using an original source	38 (1.9)	2.8 (0.6-14.1)
Total		2049 (100)	2.0 (none*-36.3)

*Journal indexed in Journal Citation Reports does not have assigned impact factor.

bmj.com
Research: How citation distortions create unfounded authority (*BMJ* 2009;339:b2680)

Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study

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Cite this as: *BMJ* 2014;348:g1996
doi: 10.1136/bmj.g1996

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g1996

STUDY QUESTION

Are people who take anxiolytic and hypnotic drugs at increased risk of premature mortality?

SUMMARY ANSWER

Prescriptions for anxiolytic and hypnotic drugs were associated with a significantly increased risk of mortality over a seven year period, after adjusting for several potential confounders.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Studies of the association between anxiolytic and hypnotic drugs and mortality have reported widely varying effect sizes. In a large cohort, such drugs were associated with a significantly increased risk of mortality, which did not seem to be entirely due to confounding by physical or psychiatric comorbidity or prescribing of other drugs.

Participants and setting

Data were based on records from 273 primary care practices contributing data to the UK General Practice Research Database. Eligible participants had to be 16 years or older, permanently registered with the primary care practice, and have at least 12 months of up to standard records. We studied three classes of drugs: benzodiazepines, Z drugs (zaleplon, zolpidem, and zopiclone), and other drugs.

Design, size, and duration

A retrospective, matched cohort study of 34 727 patients first prescribed anxiolytic or hypnotic drugs, or both, between 1998 and 2001, and 69 418 patients matched by age, sex, and practice with no prescriptions for such drugs (controls). Patients were followed-up for a mean of 7.6 years (range 0.1-13.4 years).

Main results and the role of chance

In patients prescribed these drugs, there was an overall statistically significant doubling of the hazard of death (hazard ratio 2.08), after adjusting for a wide range of potential confounders, including physical and psychiatric comorbidities, sleep disorders, and other drugs. This association remained significant and followed a dose-response pattern after restricting analyses to those with at least 12 months of follow-up and to those who were only prescribed the study drugs in the first year after recruitment (hazard ratio 1.75). Crude cumulative mortality in those given drugs was 26.46 per 100 people over the full follow-up period compared with 16.82 per 100 controls. After excluding deaths in the first year, there were approximately four excess deaths linked to drug use per 100 people followed for an average of 7.6 years after their first prescription.

Bias, confounding, and other reasons for caution

The main reason for caution is confounding by indication—study drugs may be given more often to those who are seriously ill. This was explored in the main analysis by controlling for a large number of physical and psychiatric morbidities as well as prescriptions of other drugs, and in subgroup analysis restricted to people who survived the first year (when confounding is more probable). These procedures resulted in appropriately conservative estimates, but still showed increased mortality in those prescribed study drugs. There also remains potential for residual confounding by unmeasured or incompletely measured factors, such as socioeconomic status and disease severity. These results add to evidence of an association with mortality, but must be treated with caution.

Generalisability to other populations

While overall effect sizes were broadly in keeping with most previous findings, our estimates of association were lower than those reported by one US study, which reported an adjusted hazard ratio of 4.56 over 2.5 years. All classes of drugs explored were associated with excess mortality.

Study funding/potential competing interests

This project was awarded a licence as part of a scheme operated by the UK Medical Research Council and Medicines and Healthcare products Regulatory Agency to provide data access on up to 100 000 patients. We have no competing interests.

Hazard ratios (95% confidence intervals) for age adjusted associations between defined daily doses (DDDs) of study drug and mortality before and after adjusting for other potential confounders, for exposure restricted to receipt of study drugs in first year after recruitment only and for patients with at least 12 months of follow-up

DDDs	No of patients	Age adjusted hazard ratio (95% CI)	P value	Fully adjusted* hazard ratio (95% CI)	P value
All study drugs:					
0	63 717	1.00		1.00	
1-30	5142	1.46 (1.35 to 1.57)	<0.001	1.45 (1.35 to 1.56)	<0.001
31-60	1873	2.02 (1.82 to 2.23)	<0.001	1.94 (1.76 to 2.16)	<0.001
61-90	659	2.27 (1.94 to 2.66)	<0.001	1.87 (1.59 to 2.19)	<0.001
≥91	910	3.14 (2.80 to 3.52)	<0.001	2.63 (2.34 to 2.95)	<0.001
Any DDDs	8584	1.83 (1.73 to 1.92)	<0.001	1.75 (1.65 to 1.85)	<0.001
Benzodiazepines only:					
Any DDDs	4964	1.88 (1.76 to 2.02)	<0.001	1.81 (1.68 to 1.94)	<0.001
Z drugs only:					
Any DDDs	1715	1.94 (1.72 to 2.17)	<0.001	1.78 (1.58 to 2.01)	<0.001
Other study drugs only:					
Any DDDs	1317	1.63 (1.45 to 1.82)	<0.001	1.57 (1.40 to 1.76)	<0.001

*Age, sex, physical health problems (arthritis, asthma, cancer, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, diabetes, epilepsy, gastrointestinal disorders, hypertension, musculoskeletal disorders, anxiety disorders, sleep disorders), other (non-anxiety) psychiatric disorders, and prescriptions for non-study drugs.

Antidepressant efficacy of agomelatine: meta-analysis of published and unpublished studies

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Cite this as: *BMJ* 2104;348:g1888
doi: 10.1136/bmj.g1888

This is a summary of a paper that was published on bmj.com as *BMJ* 2014;348:g1888

bmj.com
Clinical review: Depression in older adults (*BMJ* 2011;343:d5219)

STUDY QUESTION

How efficacious is the antidepressant agomelatine in the acute treatment of depression?

SUMMARY ANSWER

Agomelatine is more effective than placebo and has the same efficacy as comparator antipsychotics.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous meta-analyses have produced varied estimates of the efficacy of agomelatine because of differences in the number and type of studies included. This analysis included all completed studies of agomelatine in the acute treatment of depression and showed modest efficacy for the drug, albeit with some publication bias.

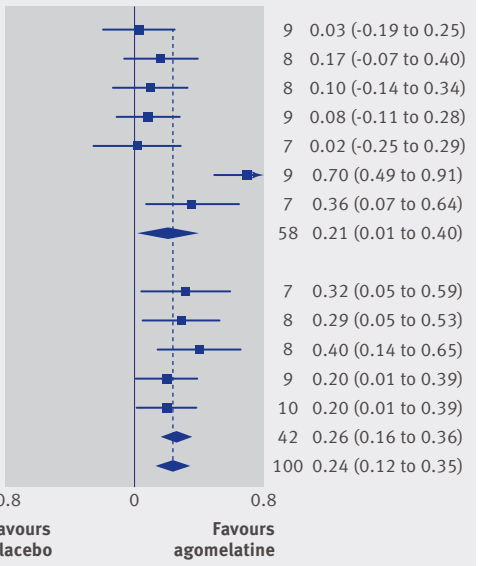
Selection criteria

Acute studies (6-12 weeks) evaluating the efficacy of agomelatine in the treatment of depression in adults were eligible for inclusion. Included studies were also randomised, double blind, and controlled (placebo and/or antidepressant). Patients met criteria for major depressive disorder (MDD) as defined by each study.

Primary outcomes

Change in mean scores on a depression rating scale at the end of treatment was the primary outcome. This was pooled as the standardised mean difference (SMD) between agomelatine and placebo/other antidepressants. Secondary outcome measures were response and remission of depression as defined by the primary studies. We also summarised tolerability data where available.

Standardised mean differences (SMD) for antidepressant efficacy of agomelatine *v* placebo



Main results and role of chance

A total of 193 records were identified. After applying eligibility criteria, 24 studies were considered for inclusion but on further examination four were excluded.

Overall, we included 20 trials (n=7460) making 12 pairwise comparisons with placebo and 13 comparisons with other antidepressants. The sources of these included studies were: eleven identified in our literature search, four more found in the EMA submission document, and full details of five further studies were provided by the manufacturer, Servier (one of which was published in full during manuscript preparation).

Twelve placebo controlled studies reported outcomes for 3951 randomised patients, which provided an intention to treat sample of 3855 patients for the primary analysis. Heterogeneity in effect sizes was substantial (I^2=66%). There was a significant difference favouring agomelatine (SMD 0.24, 95% confidence interval 0.12 to 0.35).

For secondary analyses patients were more likely to respond to agomelatine than placebo (relative risk 1.25, 95% confidence interval 1.11 to 1.41). Heterogeneity was high (I^2=63%). In 11 studies reporting remission, there was no significant difference in remission rates between the agomelatine and placebo group (1.22, 0.97 to 1.53). Again, heterogeneity was high (I^2=55%).

Thirteen comparator controlled studies (n=4559 randomised patients) were included in the primary analysis, providing an intention to treat sample of 4467. Heterogeneity between effect sizes was substantial (I^2=59%). There was no significant difference between groups (SMD 0.00, 95% confidence interval −0.09 to 0.10). Responder analysis (10 studies) showed no significant difference between groups (relative risk 1.01, 0.94 to 1.09) and with moderate heterogeneity (I^2=46%). In eight studies reporting remission there was no difference in remission rates between the two groups (relative risk 0.97, 0.79 to 1.20; I^2=67%).

Withdrawals because of adverse effects were similar for placebo (4.0%) and agomelatine (4.2%) but, in direct comparisons, less frequent for agomelatine (4.6%) than for comparator antidepressants (7.9%) (relative risk 0.61, 0.48 to 0.78).

Bias, confounding, and other reasons for caution

There was important heterogeneity in the primary and secondary outcomes, suggesting the influence of external factors. Study quality was generally good with a low but important risk of bias. In four of the included studies, change in depression rating scale score was not the primary outcome. There was substantial publication bias but no clear evidence of availability bias.

Study finding/potential competing interests

DT has received personal fees for lectures and a research grant from Servier outside the submitted work.