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Climate change and human survival

The IPCC report shows the need for “radical and transformative change”

David McCoy senior clinical lecturer, Queen Mary University, London, UK

Hugh Montgomery director, UCL Institute of Human Health and Performance, UCL, London, UK

Sabaratham Arulkumaran president, BMA, London, UK
Fiona Godlee editor in chief, BMJ, London WC1H 9JR, UK
fgodlee@bmj.com

Next week the Intergovernmental Panel on Climate Change (IPCC) will publish its report on the impacts of global warming. Building on its recent update of the physical science of global warming,¹ the IPCC's new report should leave the world in no doubt about the scale and immediacy of the threat to human survival, health, and wellbeing.

The IPCC has already concluded that it is “virtually certain that human influence has warmed the global climate system” and that it is “extremely likely that more than half of the observed increase in global average surface temperature from 1951 to 2010” is anthropogenic.¹ Its new report outlines the future threats of further global warming: increased scarcity of food and fresh water; extreme weather events; rise in sea level; loss of biodiversity; areas becoming uninhabitable; and mass human migration, conflict and violence. Leaked drafts talk of hundreds of millions displaced in a little over 80 years. This month, the American Association for the Advancement of Science (AAAS) added its voice: “the well being of people of all nations [is] at risk.”² Such comments reaffirm the conclusions of the *Lancet*/UCL Commission: that climate change is “the greatest threat to human health of the 21st century.”³

The changes seen so far—massive arctic ice loss and extreme weather events, for example—have resulted from an estimated average temperature rise of 0.89°C since 1901. Further changes will depend on how much we continue to heat the planet. The release of just another 275 gigatonnes of carbon dioxide would probably commit us to a temperature rise of at least 2°C—an amount that could be emitted in less than eight years.⁴

“Business as usual” will increase carbon dioxide concentrations from the current level of 400 parts per million (ppm), which is a 40% increase from 280 ppm 150 years ago, to 936 ppm by 2100, with a 50:50 chance that this will



Mass migrations predicted

deliver global mean temperature rises of more than 4°C. It is now widely understood that such a rise is “incompatible with an organised global community.”⁵

The IPCC warns of “tipping points” in the earth's system, which, if crossed, could lead to a catastrophic collapse of interlinked human and natural systems. The AAAS concludes that there is now a “real chance of abrupt, unpredictable and potentially irreversible changes with highly damaging impacts on people around the globe.”²

And this week a report from the World Meteorological Office (WMO) confirmed that extreme weather events are accelerating. WMO secretary general Michel Jarraud said, “There is no standstill in global warming . . . The laws of physics are non-negotiable.”⁶

Mayday

This is an emergency. Immediate and transformative action is needed at every level: individual, local, and national; personal, political, and financial. Countries must set aside differences and work together as a global community for the common good, and in a way that is equitable and sensitive to particular challenges of the poorest countries and most vulnerable communities.

What we all do matters, not least in how it influences others. Those who profess to care for the health of people perhaps have the greatest responsibility to act. And there are signs of action being taken. Within the health system, organisations and health facilities are reducing their carbon footprint. Barts Health NHS Trust has, for example, reduced its energy bill by 43% since 2009. The president of the World Bank, Jim Yong Kim, himself a public health physician, has called for divestment from

fossil fuels and investment in green energy.⁷ We should all respond.

Such action not only limits the threats of climate change, but could offer a health dividend, including potentially large financial savings for health systems. More active forms of transport and the consumption of less red meat will cut death and illness from cardiovascular disease, obesity, diabetes, and cancer. Less air pollution will cut the global burden of asthma, chronic obstructive pulmonary disease, cancer, and heart disease.³ The IPCC has incorporated this new understanding into its latest report on impacts, and we can expect to see this message flowing into the World Health Organization's plans for action, to be discussed at its climate conference in August.

So what can health professionals do? Firstly, we should push our own organisations (universities, hospitals, primary care providers, medical societies, drug and device companies) to divest from fossil fuel industries completely and as quickly as possible, reinvest in renewable energy sources, and move to “renewable” energy suppliers. Secondly, we should each use whatever influence we have to change the minds and behaviour of others who are in positions of influence.

Thirdly, we need to build an alliance of medical and other health professionals to speak clearly to the public, the media, governments, and intergovernmental bodies to provide a strong and unified message—that climate change is real and is the result of human activity; that it is already affecting people around the world and is the greatest current threat to human health and survival; and that there are many positive and practical things we can do systematically and at scale to avert its worst effects.⁸

If we are to avoid catastrophic climate change and bequeath a sustainable planet worth living on, we must push, as individuals and as a profession, for a transformed, sustainable, and fair world.

For more information on what health professionals can do in support of the IPCC's report and to learn more about the implications of the report for human health, visit: www.climateandhealthalliance.org/resources/ipcc-resources.

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Research: Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy (*BMJ* 2009;338:b1081)

Helping pregnant smokers to quit

Behavioural support works, evidence on drug treatment still patchy

Leonie S Brose lecturer in addictions, UK Centre for Tobacco and Alcohol Studies, Institute of Psychiatry, King's College London leonie.brose@kcl.ac.uk

Not all smokers manage to quit during pregnancy. In England, 26% of women smoke in the year before their pregnancy and 12% smoke through to delivery.¹ The rate is similar in other high income countries, whereas in low and middle income countries, smoking rates are more variable and seem to be increasing among young women.² In addition to the countless negative consequences for the smoker's own mental and physical health, smoking in pregnancy is linked to a wide range of poor health outcomes for the child.³ Thus there is an urgent need to help pregnant smokers who find it difficult to quit.

Nicotine replacement therapy (NRT) is effective in smokers in general,⁴ but a recent review of randomised controlled trials found no good evidence in pregnant women.⁵ In the linked paper, Berlin and colleagues report a welcome randomised placebo controlled trial that found no benefit of transdermal nicotine patches in pregnant smokers.⁶ Recruitment seems to have been slow, but with over 400 participants this is the second largest trial of NRT in pregnancy to date.

Compared with previous trials, Berlin and colleagues' study had several advantages. In an attempt to match participants' nicotine intake to that achieved by smoking, a substantial proportion of the participants received higher doses of NRT than in previous trials. Adherence to treatment was high. Additionally, the patches were administered from quit date to delivery, providing a longer duration of treatment than in previous trials, and participants were advised to continue treatment even if they restarted smoking.

Despite this careful design, the patches did not seem to increase smoking abstinence from quit date to delivery, an outcome stringently assessed by self reported abstinence confirmed by levels of carbon monoxide in expired air.

Limitations of the new trial were that treatment could start only in the second trimester, only participants who could not quit unaided could be included, and there was a gap of two weeks after the first session before the next session of behavioural support and adjustment of NRT. This time delay is crucial as it covers the period when smokers are generally at most risk of relapse, borne



DAVID GREEN/LAMY

Tell her about the teratogens

out by figures in this study. This delay perhaps explains why both groups had low success rates.

Hard evidence on the effectiveness and efficacy of drug treatments for pregnant smokers is lacking. Whereas other smokers can choose from a range of effective options, such as bupropion, varenicline, and cytosine, these agents have not been evaluated in pregnant women and cannot be recommended for this group. Of all the available NRT products and delivery modes, Berlin and colleagues chose transdermal patches. In non-pregnant smokers, combining patches with faster acting forms of NRT works substantially better than using patches alone.⁴⁻⁷ These combinations are more flexible, help target cravings better, and are commonly used in practice. To date, no trials have studied combination treatments in pregnant smokers; however, data from clinical practice strongly suggest a benefit of combined NRT over single forms.⁸

Psychosocial interventions work better

Fortunately, and in contrast with disappointing results and a slim evidence base for drug treatment, good evidence shows that psychosocial interventions help pregnant smokers to quit. Effective, evidence-based strategies include individual counselling, financial incentives, peer support, and feedback on fetal health or the by-products of tobacco smoking (for example, measuring the levels of carbon monoxide

in expired air).⁹ Counselling and feedback work best when delivered in combination and tailored to individual women. Although financial incentives had the largest effect sizes in a recent systematic review,⁹ this particular result should be interpreted with caution as it was based on few trials with small samples. Most of the included studies evaluating psychosocial interventions were from high income countries, leaving a major gap in the evidence about how best to support pregnant women trying to quit smoking in low and middle income countries.

Further research has analysed trial and treatment protocols of these efficacious interventions and identified the active ingredients.¹⁰ The behavioural support offered to women in Berlin and colleagues' trial included some of these, but such support was not based on a comprehensive manual and important elements are likely to have been omitted. Again, we know that psychosocial support is critical in the first few weeks of a quit attempt,¹¹ which was when the participants in the present study did not receive any.

So how does this affect practitioners supporting pregnant smokers? They should routinely intervene with all smokers. There is no need to ask whether a smoker wants to stop smoking before offering advice and help.¹²⁻¹³ This advice should be followed by a referral to specialist smoking cessation services or instigation of other intensive and evidence based behavioural support. Given the limitations of the new trial and the potential benefit of combination therapy, it may be too early to abandon the option of NRT entirely.

Pregnant smokers are exposing their fetuses not only to nicotine but also to a multitude of other potentially teratogenic substances in tobacco smoke. If effective, nicotine substitution using established NRT or other delivery systems would be a far safer alternative. However, a much greater effort is still needed to identify, test, and deliver more effective treatments for pregnant smokers who struggle to quit.

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RESEARCH, p 11

Agomelatine may work slightly better than a placebo, but its effect size is well below NICE's threshold for clinical relevance

Does agomelatine have a place in the treatment of depression?

Seems to work no better than more established and commonly used antidepressants

Gilles Ambresin senior lecturer, honorary research fellow
gilles.ambresin@chuv.ch

Jane Gunn chair of primary care research, General Practice and Primary Health Care Academic Centre, University of Melbourne, Carlton, Victoria, Australia

Depression is mainly managed in primary care,^{1 2} and antidepressant medication is the most common treatment used in this setting in the developed world.³ Current clinical guidelines recommend that primary care doctors consider prescribing antidepressants for adults with major depressive disorder and dysthymia.^{4 5} Recent research suggests that the efficacy of antidepressants may have been overestimated because of publication bias—the tendency for positive trials to have a higher likelihood of publication than negative trials.^{6 7} While some criticism remains about the analytical techniques used, in particular by Kirsch et al,⁸ the balance of evidence does support the view that the benefits of these agents have been overestimated and further suggests that they are more effective for people with severe depressive disorder and less effective for those with mild to moderate depressive disorder.

These findings have important implications for primary care, where most depression is managed, and paves the way for research into new and more effective treatments. Agomelatine, which acts via the melatonergic system, has been promoted as an alternative to second generation antidepressants (selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors) with a different side effect profile.⁹

In a linked paper, Taylor and colleagues examine the efficacy of agomelatine using both published and unpublished studies.¹⁰ Agomelatine has already generated much debate and interest, including three other published meta-analyses.^{9 11 12} A previous meta-analysis considering only published studies found that agomelatine was superior to placebo (effect size 0.26, 95% confidence 0.15 to 0.34) and to comparator drugs (effect size 0.11, 0.02 to 0.17).¹¹ Head to head comparisons between agomelatine and venlafaxine, sertraline, fluoxetine, paroxetine, or escitalopram reported a greater

reduction in scores on the Hamilton depression rating scale (score 0-50) with agomelatine than with second generation antidepressants (difference in score reductions 0.86, 0.18 to 1.53).⁹

A recent meta-analysis that included unpublished studies reported a greater reduction in symptoms scores with agomelatine than with placebo (difference in score reductions 1.51, 0.73 to 2.29).¹² Although these findings provide statistical evidence that agomelatine is more effective than placebo and some other antidepressants, the size of the benefit looks small and may not be clinically relevant. It is generally accepted that an effect size of 0.8 is large in clinical terms, 0.5 is medium, and 0.2 is small.¹³

Taylor and colleagues used a systematic review strategy in addition to working with the European Medicines Agency and manufacturers of agomelatine to identify all relevant published and unpublished studies. They identified 20 trials including 8322 participants that met inclusion criteria and performed a meta-analysis to determine treatment effect estimates. Results show that agomelatine is more effective than placebo (effect size 0.24, 0.12 to 0.35) and has similar efficacy to comparator antidepressants (effect size 0.00, -0.09 to 0.10) as measured by differences on symptom rating scales for depression. Agomelatine was associated with higher response rates than placebo (relative risk of response 1.25, 1.11 to 1.41) but not with higher remission rates. Agomelatine improved neither of these outcomes when compared with other antidepressant drugs.

Importance of unpublished studies

This study underlines the importance of including both published and unpublished studies in any meta-analysis evaluating antidepressants. Examination of published studies alone overestimated the efficacy of agomelatine by 20%. This overestimate is similar to the influence of publication bias that has been reported for most of the commonly used antidepressants.⁶

Agomelatine is no more effective than other agents, and, while it may work slightly better than a placebo, the effect size reported by Taylor and colleagues is well below the threshold for clinical relevance of

0.50 adopted by England's National Institute for Health and Care Excellence (NICE).⁵ Patients with depression cross this threshold for effect size when they score 27 on the Hamilton depression rating scale,¹⁴ which indicates that antidepressants are better than a placebo only for those with severe initial symptoms. The vast majority of studies in the new meta-analysis recruited patients with scores of at least 22 (severe symptoms).¹⁴ These findings have important implications for the use of antidepressants in primary care, where most patients seeking help for depression have only mild or moderate symptoms. People taking agomelatine need repeated monitoring of their liver enzymes, which further limits the cost effectiveness of this drug in practice. There is more work to be done in exploring the harms associated with treatment.

How should primary care doctors respond to recent evidence that antidepressants are less effective for mild or moderate major depressive disorder, and that overall efficacy has been overestimated? Recent recommendations from the Netherlands advise doctors to provide psychoeducation to patients who are depressed and, if necessary, offer a short psychological treatment first.¹⁵ Is this recommendation evidence based? A recent meta-analysis of 117 trials compared psychotherapy with control conditions (mainly usual care, placebo, or waiting list).¹⁶ Results showed a mean effect size of 0.67 favouring psychotherapy (95% confidence interval 0.60 to 0.75), which was reduced to 0.42 (0.33 to 0.51) after adjustments for publication bias—just below the accepted cut-off value for a moderate and clinically relevant effect size (0.5).

Some primary care doctors may find it difficult to reconcile these findings with their clinical experience of patients who achieve a speedy remission once they start taking antidepressants. Further research could usefully explore whether some people are more likely to respond to antidepressants than others. Large datasets will be required to test the possible contribution of factors such as sex, genes, or biomarkers.

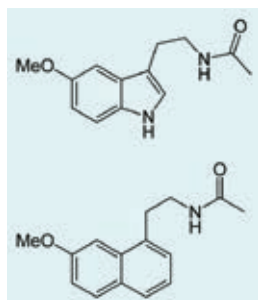
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RESEARCH, p 14



Melatonin (top) v agomelatine

WIKIPEDIA

Wikipedia's infrastructure is particularly good for teaching contributors the difference between primary, secondary, and tertiary sources and encouraging researchers to cite secondary sources such as review articles in preference to anything else

Citing Wikipedia

Don't do it—Wikipedians wouldn't

Lane Rasberry Wikipedian in residence, Consumer Reports, 101 Truman Avenue, Yonkers, NY 10703, USA
 lrasberry@consumer.org

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In a linked study,¹ Bould and colleagues found more than 1400 health science articles that cited Wikipedia, with half of the citations occurring between 2010 and 2013. They categorized each citation by type and judged that just 4% of citations were appropriate—in other words, categorized as “citations about Wikipedia” or “Wikipedia used in methods.” The headline message, which I believe to be true, is that Wikipedia is being cited unjustifiably with sufficient frequency to constitute a problem that merits a response from the academic community. The citing of Wikipedia not only shows a lack of recognition that Wikipedia is not a good source for citation but also signals a greater concern that some readers are failing to apply critical thinking to judge the quality of information they encounter.

Bould and colleagues conclude that health science journals should be cautious about publishing papers that cite Wikipedia. I also hope that this paper encourages researchers to spread the word, already accepted by the Wikipedia community, that Wikipedia is not to be cited in health science articles, or anywhere else. Perhaps researchers and academics cite Wikipedia not knowing that the content is compiled by anonymous contributors over the internet with no formal oversight. In which case, Wikipedians need to be clearer about the provenance of Wikipedia content. Alternatively, people may be citing Wikipedia while knowing that it is not authoritative, possibly because it has some special citation appeal



Look, but don't touch (unless it's to add original sources)

not shared by other inappropriate sources. A final possibility is that all kinds of people, including academic authors, put faith in media without sufficiently considering the reliability of what they read or cite. If that is the case, then perhaps serious reflection is warranted in academia, research, and education generally. Bould and colleagues' findings indicate that we should all support each other in being vigilant to raise research standards.

Wikipedia's popularity tells me, as an enthusiastic contributor, that people are keen to learn and like having their information reliably sourced to credible research publications. Everyone who lives in an information environment influenced by Wikipedia should be aware that it is an online encyclopedia published within a platform that encourages its readers to make modifications to the publication as they read it. Anyone at any time can click the “edit” button at the top of any Wikipedia article and then change it as they like.

In traditional reference works, having personal authorship by experts is the main quality control strategy. Historically, publishers sought to avoid publishing anything written by unknown people with dubious credentials. Thanks to this precedent, some people may assume that information is dependable even though it is not offered in the same way by Wikipedia or by many other channels of new media.

Respect for original sources

Wikipedia publishes through a structure of anonymous volunteer authors, so its strategy for maintaining integrity is to request exhaustive citing of sources for the information it presents. As a summary of published thought, Wikipedia does not publish anyone's original ideas or new interpretation. This design recruits readers who respect and defer to the original sources by strongly encouraging them to check the veracity of what they see

by following citations. Also, as readers check a Wikipedia citation, they are automatically asked by the Wikipedia community either to endorse (by inaction) Wikipedia's text if they agree with it or to change the text if they find that it does not agree with the original source. This is how Wikipedia maintains its quality and integrity.

Wikipedia's pervasiveness, as documented in the linked paper,¹ could be an opportunity for increased collaboration between the Wikipedia community and academia. Wikipedia is already the rare project that collects the leisure time of volunteers who enjoy discussing the relative merit of sources and championing the correct use of citations. Wikipedia's infrastructure is particularly good for teaching contributors the difference between primary, secondary, and tertiary sources and encouraging researchers to cite secondary sources such as review articles in preference to anything else.

Anyone who wants to learn more about the Wikipedia project can post questions to Wikipedia's Reliable Sources Noticeboard (https://en.wikipedia.org/wiki/Wikipedia:Reliable_sources/Noticeboard), the Wikipedia Education Program (https://en.wikipedia.org/wiki/Wikipedia:Education_program), which does outreach to universities, or the WikiProject Medicine forum (https://en.wikipedia.org/wiki/Wikipedia:WikiProject_Medicine); or, better, they can add something to a health science article in Wikipedia and see the response. All are welcome.

Everyone should try to have research practices at least as good as those of the Wikipedians, and they would never cite Wikipedia. Competing interests and references are in the version on bmj.com. Provenance and peer review: Commissioned; not externally peer reviewed.

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