The problem of orphan drugs

Incentives to make orphan drugs should be proportionate to their benefits

FEATURE, p 1076
ANALYSIS, p 1084

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Amifampridine (3,4-diaminopyridine phosphate) is approved for Lambert-Eaton syndrome under laws designed to encourage manufacturers to develop drugs for life threatening or chronically debilitating rare disorders—"orphan diseases."[1 2] It costs up to £44 200 (€52 000; $71 300) per patient each year. When bought from chemical suppliers, the equivalent dose of 3,4-diaminopyridine base costs £280. The clinical evaluation of the product relies on published literature that refers mainly to clinical experience with the free base form of 3,4-diaminopyridine.[3] The European Union legislation under which it is licensed allows medicines to be designated "orphan drugs" during development, receive financial benefits before approval, and have several years free from competition if granted a marketing authorisation (licence).

The intention of orphan drug legislation in the United States and Europe—put bluntly—is to make the development of drugs for orphan diseases profitable. The unintended consequence is exploitation of the rules for profit. Like tax avoidance, this is legal, but not necessarily desirable.

The regulations can be exploited in different ways. Drugs can be licensed successively for several orphan disorders[4]: imatinib is indicated for seven separate rare malignancies. Medicines already marketed can be licensed for an orphan disease and remarketed: it costs £160 a year to treat a patient with sickle cell disease using 500 mg capsules of hydroxycarbamide (hydroxyurea) licensed for chronic myeloid leukaemia, but it costs £14 900 a year using 1 g tablets of hydroxycarbamide licensed as an orphan drug for sickle cell disease. Oral ibuprofen for analgesia costs £0.08 per gram, but intravenous ibuprofen for patent ductus arteriosus costs £6575 per gram. This is tens or hundreds of times more than the cost of producing sterile ibuprofen solution for intravenous injection in an NHS facility. Diclofenac, which does not have orphan status, costs £0.11 per gram in tablet form and £4.80 per gram as an injection.

There is virtue in a drug having a marketing authorisation because it assures pharmaceutical quality and pharmacovigilance, and it places liability for harm on the holder of the marketing authorisation. However, the regulations are less stringent for orphan drugs, and in many cases, including that of amifampridine, applicants for a licence do not need to conduct prelicensing clinical trials but can rely on pre-existing data that often come from publicly funded research.

Prescribing expensive licensed drugs when cheaper and effective alternatives exist inflates the costs of care, and—because resources are finite—other patients suffer. In the United Kingdom, doctors are discouraged from prescribing unlicensed drugs. The General Medical Council (GMC) requires them to "be satisfied that an alternative, licensed medicine would not meet the patient's needs."[5] The Medicines and Healthcare Products Regulatory Agency states that "all medicines must have a marketing authorisation unless exempt."[6] The Royal Pharmaceutical Society discourages the manufacture of unlicensed medicinal products ("specials") when licensed products exist.[7] Doctors are consequently reluctant to prescribe, and pharmacists to supply, products that are cheap and effective. This is the case even for non-orphan drugs. For example, nifedipine licensed for treatment of hypertension is an effective oral tocolytic and costs just over £1 per patient, but the licensed intravenous tocolytic, atosiban, costing 400 times as much, is often used instead.

The costs of drugs in the United Kingdom fall on the NHS. But in the US, where many patients have to pay, most chose unlicensed bevacizumab for age related macular degeneration ($75 per dose) rather than ranibizumab ($2000 per dose).[8]

The utilitarian view values health gain for common and rare diseases equally.[9] The current incentives to licence drugs for rare diseases in effect put more value on health improvement in rare diseases than in common ones.[1] Waxman argued that such a strategy was necessary to overcome the financial disincentives to developing treatments for rare disorders that exist in a free market. There is presumed public support for this view, although a recent study failed to find evidence for it.[10] The incentives are now too generous.[11] The drug industry should be encouraged to make innovative drugs for rare diseases but accept value based pricing when it arrives in the next Pharmaceutical Price Regulation Scheme.[12] Repackaged, rebranded, or recycled drugs merit little reward. The NHS could, and should, make and distribute "specials" for rare diseases, as the Agence Générale des Equipements et Produits de Santé does in Paris. And in the interest of all patients, the GMC should allow doctors to prescribe a drug that meets the individual patient's needs but is not licensed for the specific indication, even if a licensed medicine exists for the same indication.

1 Waxman HA. The history and development of the Orphan Drugs Act. In: Scheinberg IH, Walshe JM, eds. Orphan drugs and orphan diseases. Manchester University Press/Fulbright Commission. 1986.
2 Regulation (EC) No 141/2000 of The European Parliament and of the council of 16 December 1999 on orphan medicinal products. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF.
3 European Medicines Agency. European public assessment report. Firdapse. 2009. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001032/WC500069918.pdf.
4 Braun MM, Farag-El-Massah S, Xu K, Coté TR. Emergence of orphan drugs in the United States: a quantitative assessment of the first 25 years. *Nat Rev Drug Discov* 2020; online 7 June; doi:10.1038/nrd3160.
5 General Medical Council. Supplementary guidance: good practice in prescribing medicines. 2008. www.gmc-uk.org/static/documents/content/Good_Practice_in_Prescribing_Medicines_0911.pdf.

6 Medicines and Healthcare Products Regulatory Agency. Guidance note 14. The supply of unlicensed relevant medicinal products for individual patients. MRHA, 2008.
7 Royal Pharmaceutical Society. Dealing with specials. *Pharmacy Professional* June 2010; 27-32. www.rpharms.com/support-pdfs/ppjune2010-specials.pdf.
8 Folk JC, Stone EM. Clinical therapeutics: ranibizumab therapy for neovascular age-related macular degeneration. *N Engl J Med* 2010;363:1648-55.
9 McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the National Health Service: should we value rarity? *BMJ* 2005;331:1016-9.
10 Desser AS, Gyrd-Hansen D, Olsen JA, Grepperud S, Kristiansen IS. Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. *BMJ* 2010;341:c4715.
11 Hughes D. Rationing of drugs for rare diseases. *Pharmacoeconomics* 2006;24:315-6.
12 Ferner RE, Hughes DA, Aronson JK. NICE and new: appraising innovation. *BMJ* 2010;340:b5493.

Suicide attempts in people taking isotretinoin for acne

Are increased, but the risk is difficult to separate from the higher risk associated with the condition itself

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RESEARCH, p 1090

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In the linked study, Sundström and colleagues assess the association between isotretinoin (13-*cis*-retinoic acid) taken by people with severe acne and attempted suicide.[1] Isotretinoin is effective for severe nodulocystic or treatment resistant acne, but its use is controversial. Isotretinoin is associated with considerable mucocutaneous side effects, other adverse effects, and a high risk of teratogenicity, but it is the putative links with depression and suicide that have generated most unease in users, potential users, and their families.[3]

Concerns about an association with suicide and depression were initially prompted by case reports and case series.[4] Although a causative association is biologically plausible,[5] epidemiological studies have generally failed to find one. Analysis of data from the Canadian health database and the UK general practice database found no increase in depression, attempted suicide, or suicide in people with acne who used isotretinoin compared with those who used antibiotics and no changes in these outcomes before and after treatment with isotretinoin.[6] In addition, in a study of Finnish male military conscripts isotretinoin was not associated with increased suicidal ideation.[7] With regard to depression, a US retrospective analysis of isotretinoin and antidepressant prescriptions found no association, but a Canadian analysis of prescriptions and hospital admissions did find a significant association.[8 9]

It is difficult to tease out the relation between mental health and isotretinoin because acne itself is associated with psychiatric morbidity,[10] including depression.[11] Furthermore, evidence exists that treatment of acne with isotretinoin improves depression scores.[12] Acne itself may be associated with suicidal ideation and attempted suicide.[10 11]

Given this uncertainty, Sundström and colleagues' retrospective cohort study of suicide attempts up to three years before treatment, during treatment, and up to 15 years after treatment with isotretinoin is important.[1] The authors found an increased risk of suicide attempts in those taking isotretinoin and that this risk peaks in the months after the start of treatment. Using standardised incidence ratios (observed number divided by expected number of suicide attempts standardised by sex, age, and calendar year) for attempted suicide, they found a significantly increased risk during and six months after the end of treatment for the first attempt (standardised incidence ratios 1.93, 95% confidence interval 1.08 to 3.18) and for all attempts (1.78, 1.04 to 2.85). They did not interpret this as evidence of a causal association, however. Intriguingly, the risk of attempted suicide was already rising in the three years before treatment was started (although not significantly) and returned to normal within three years after treatment.

These findings (together with recent evidence from a Norwegian population based study for an association of acne with suicidal ideation[10]) could be interpreted to mean that acne confers an increased risk of attempting suicide (an increased risk that attenuates in the years after successful isotretinoin treatment). The increased risk of attempted suicide during treatment might also be acne related rather than treatment related, or at least might not be related to the proposed effects of isotretinoin on the central nervous system. For example, isotretinoin is often associated with an initial severe worsening of acne. Also, as Sundström and colleagues point out,[1] people whose high expectations of treatment are not met or those in whom improvement in acne does not produce the expected social benefits may experience negative psychological sequelae unrelated to isotretinoin's biological actions. Of course, the increased risk may be multifactorial.

Clinicians can draw important practical conclusions from this study, which are relevant whether isotretinoin is or is not, directly or indirectly, causally implicated in suicide. During and after treatment with isotretinoin (perhaps, especially, unsuccessful treatment), patients should be carefully monitored for depression and suicidal thoughts. Patients probably have an increased risk before treatment, however, so all patients with acne of a severity for which isotretinoin is indicated should have psychosocial factors and suicidal intent monitored.

Who should do this monitoring? In most countries dermatologists prescribe isotretinoin and perform the quite rigorous monitoring. General practitioners have more appropriate training and experience in psychological medicine, however, and could add invaluable expertise in the psychological aspects of management in a shared care model with dermatologists. Given the extended period of risk, families of patients may also have a role in this monitoring.

Sundström and colleagues' study also provides valuable insights into the absolute risk of treatment with isotretinoin. The authors calculate a number needed to harm for a standard six month course of isotretinoin of 2300 for a first suicide attempt and 5000 per year for a repeat attempt.

Acne, especially acne of the severity for which isotretinoin is indicated, is not a trivial condition. These numbers must be considered in the context of the often marked psychosocial harm and propensity to scar associated with acne itself.

1 Sundström A, Alfredsson L, Sjölin-Forsberg G, Gerdén B, Bergman U, Jokinen J. Association of suicide attempts with acne and treatment with isotretinoin: retrospective Swedish cohort study. *BMJ* 2010;341:c5812.
2 Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA* 2004;292:726-35.
3 Magin P, Adams J, Heading G, Pond D, Smith W. Patients' perceptions of isotretinoin, depression and suicide. A qualitative study. *Aust Fam Physician* 2005;34:795-7.
4 Wysowski DK, Pitts M, Beitz J. An analysis of reports of depression and suicide in patients treated with isotretinoin. *J Am Acad Dermatol* 2001;45:515-9.
5 Bremner JD, McCaffery P. The neurobiology of retinoic acid in affective disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32:315-31.
6 Jick S, Kremers H, Vasilakis-Scaramozza C. Isotretinoin use and risk of depression, psychotic symptoms, suicide and attempted suicide. *Arch Dermatol* 2000;136:1231.
7 Rehn LMH, Meririnne E, Hook-Nikanne J, Isometsa E, Henriksson M. Depressive symptoms and suicidal ideation during isotretinoin treatment: a 12-week follow-up study of male Finnish military conscripts. *J Eur Acad Dermatol Venereol* 2009;23:1294-7.
8 Hersom K, Neary MP, Levaux HP, Klaskala W, Strauss JS. Isotretinoin and antidepressant pharmacotherapy: a prescription sequence symmetry analysis. *J Am Acad Dermatol* 2003;49:424-32.
9 Azoulay L, Blais L, Koren G, LeLorier J, Berard A. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008;69:526-32.
10 Halvorsen J, Stern R, Dalgard F, Thoresen M, Bjertness E, Lien L. Suicidal ideation, mental health problems, and social impairment are increased in adolescents with acne: a population-based study. *J Invest Dermatol* 2010; published online 16 September; doi:10.1038/jid.2010.264.
11 Purvis D, Robinson E, Merry S, Watson P. Acne, anxiety, depression and suicide in teenagers: a cross-sectional survey of New Zealand secondary school students. *J Paediatr Child Health* 2006;42:793-6.
12 Kaymak Y, Taner E, Taner Y. Comparison of depression, anxiety and life quality in acne vulgaris patients who were treated with either isotretinoin or topical agents. *Int J Dermatol* 2009;48:41-6.

Doctors and climate change

Links between climate policy and health policy must not be overlooked

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In November 2010, representatives from countries around the world will meet in Cancún, Mexico, at the 2010 United Nations Climate Change Conference.[1] Here they will attempt to draft a treaty aimed at stabilising atmospheric greenhouse gas concentrations at a level that will prevent catastrophic climate change. What a pity the meeting had not been scheduled in Pakistan. Then the anger of those whose livelihoods have been destroyed by the biblical floods that have washed away the hopes of a nation would surely have focused the delegates' minds. Alternatively, the meeting could have been held in western Russia, where record high temperatures, wild fires, droughts, and crop failures have precipitated a state of emergency. The conference might even have been held in Mozambique, where rapidly rising wheat prices have caused rioting in the streets. All of these climatic events and their predictable human aftermath occurred this year and all are made more probable by climate change, the main cause of which is the increase in anthropogenic greenhouse gas emissions, mostly from the burning of fossil fuels.

But perhaps Mexico is not such a bad location for the climate conference after all. Mexico is second only to the US with regard to the prevalence of obesity. One in four Mexicans is obese.[2] If the delegates at the climate conference think that obesity and climate change are unrelated, they would be wrong. The planet is getting hotter, its people are getting fatter, and the use of fossil fuel energy is the cause of both.[3] Large increases in motor vehicle traffic in Mexican towns and cities have decimated levels of physical activity. This, combined with increased availability of energy dense food, has propelled the body mass index in the entire population upwards. Mexicans are paying for these changes in terms of reduced health and wellbeing, with increased rates of diabetes, heart disease, stroke, and cancer. Unchecked car use has also conspired with rapid population growth and topology to make Mexico City one of the most polluted cities in the world. The city topped the list in a 2010 IBM poll of commuter pain, with 22% of commuters spending more than two hours a day travelling to and from work.[4] In this respect, the people of Mexico stand shoulder to shoulder with the people of Pakistan as victims of the use of fossil fuel energy.

Health professionals everywhere have a responsibility to put health at the heart of climate change negotiations. Firstly, because climate change already has, and will continue to have, a major adverse impact on the health of human populations.[5] Secondly, because reducing greenhouse gas emissions has unrivalled opportunities for improving public health.[6] Indeed, moving to a low carbon economy could be the next great public health advance. The hazards to human health from climate change are well documented. Strong evidence already exists that climate change will affect rates of malnutrition, diarrhoea, malaria, deaths as a result of floods, and temperature related deaths from cardiovascular disease.[5]

More recently, the health benefits of reducing greenhouse gas emissions have been assessed and quantified. Meeting greenhouse gas emissions targets in the transport sector will require substantial increases in walking and cycling, with corresponding reductions in car use.[7] The available epidemiological evidence linking physical activity and health has shown that this would dramatically reduce rates of chronic disease, with around a 10-20%

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reduction in ischaemic heart disease and stroke, 12% reduction in breast cancer, 8% reduction in dementia, and 6% reduction in depression.[7] This last estimate considered the effects of physical activity only. It did not take into account the mental health benefits of urban greening, reduced community severance, reduced fatness, and less noise.

The project also considered the health effects of reducing livestock production to limit the cattle related methane emissions and deforestation that are contributing to global warming.[8] A reduction in animal products in the diet would reduce consumption of saturated animal fats and result in a large (about 15%) fall in ischaemic heart disease. Reducing meat consumption might also reduce rates of cancer of the colon and rectum. Colorectal cancer is the second most common cancer in men after lung cancer and meat consumption is an established risk factor. Eating less saturated fat and taking more physical activity will reduce levels of population fatness. Consuming less animal products will also reduce food prices because cattle are fed on grain and high meat consumption forces up world grain prices. Feeding grain to animals is an inefficient use of food energy in a world where millions of people go hungry.[9]

A reduction in car use would also affect food prices. In April 2008, Evo Morales, president of the poor and increasingly hungry Bolivia, pleaded "la vida primero los autos segundos" (life first, cars second), exhorting the wealthy world to stop burning food in their cars. He was objecting to Western governments' policies on biofuels for transport. However, car use and food prices were linked long before the introduction of biofuels. Car use drives up food prices because oil is a key agricultural input. A reduction in car use is essential to prevent starvation.

Responding to climate change could be the most important challenge that health professionals face. The Climate and Health Council was established to enable health professionals around the world to take personal and collective action against the causes of climate change, and to insist that global health is central in climate change negotiations.[10] It seeks to provide information on all aspects of health and climate change and suggests a range of actions that health professionals can take. We invite colleagues everywhere to join us in tackling this major public health scourge of the 21st century. By signing the Climate and Health Council pledge (www.climateandhealth.org/pledge), you will join the thousands of health professionals already committed to action. Please contact your health minister to ensure that the links between climate policy and health policy are known and fully taken into account at COP16 in Cancún, COP17 in South Africa next year, and indeed in all climate change negotiations.

1 UNFCCC. The United Nations Climate Change Conference in Cancun, 29 November-10 December 2010.http://unfccc.int/meetings/cop_16/items/5571.php.
2 Ruiz-Arregui L, Castillo-Martínez L, Orea-Tejeda A, Mejía-Arango S, Miguel-Jaimes A. Prevalence of self-reported overweight-obesity and its association with socioeconomic and health factors among older Mexican adults. *Salud Pública Méx* 2007. www.scielosp.org/scielo.php?script=sci_arttext&pid=S0036-36342007001000007.
3 Roberts I, Edwards P. The energy glut: the politics of fatness in an overheating world. Zed Books, 2010.
4 Goldsmith B. IBM finds world's worst commutes. Toronto Sun 2010. www.torontosun.com/life/2010/06/30/14564796.html.
5 McMichael A, Woodruf R, Hales S. Climate change and human health: present and future risks. *Lancet* 2006;367:859-69.
6 Haines A, Wilkinson P, Tonne C, Roberts I. Aligning climate change and public health policies. *Lancet* 2009;374:2035-8.
7 Woodcock J, Edwards P, Tonne C, Armstrong BG, Ashiru O, Banister D, et al. Public health benefits of strategies to reduce greenhouse-gas emissions: urban land transport. *Lancet* 2009;374:1930-43.
8 Friel S, Dangour AD, Garnett T, Lock K, Chalabi Z, Roberts I, et al. Public health benefits of strategies to reduce greenhouse-gas emissions: food and agriculture. *Lancet* 2009;374:2016-25.