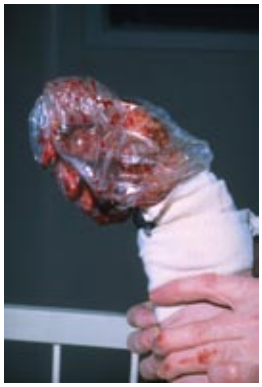
Prophylaxis with systemic antibiotics in patients with severe burns

In the absence of good quality evidence, caution is advised



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RESEARCH, p 517

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In the linked systematic review and meta-analysis, Avni and colleagues assess the evidence for giving antibiotic prophylaxis to patients with severe burns.[1] The authors find that the quality of the evidence is poor, so robust conclusions cannot be drawn.

Burn injuries disrupt the primary barrier between sterile tissues and the colonised external world, and they severely compromise the host's defences so that micro-organisms multiply and penetrate deeper into the tissues. Despite the use of dressings, burned skin becomes necrotic tissue that is constantly exposed to the environment and is an ideal medium for micro-organisms to grow.

Aggressive removal of devitalised or infected tissues in burn wounds is vital to the success of reconstructive surgery. However, it is impossible to maintain a sterile environment, and endogenous flora are progressively altered by acquisition of external organisms through contact with materials, the environment, and healthcare workers. The addition of a warm and moist environment, repeated surgery, and long term treatment with antibiotics allows resistant micro-organisms to emerge, with secondary contamination of the environment and potential spread to other patients.[2] Outbreaks of meticillin resistant *Staphylococcus aureus*, multiresistant Gram negative bacilli (such as *Acinetobacter* and *Pseudomonas*), or non-albicans *Candida* spp are common in burn units.[3] In critically ill patients, the highest rates of nosocomial infections are seen in those with burns, in whom these infections can contribute to as much as 75% of the deaths that occur after initial resuscitation.[4]

The use of antibiotics in patients with severe burns is challenging. Several infectious episodes are common, and wound infection is difficult to diagnose (criteria include worsening clinical signs of sepsis and positive cultures of surgical biopsies).[5] Prompt treatment of sepsis or any nosocomial infection related to a device is mandatory. Overexposure to antibiotics (too long or administration of an antibiotic with too broad a spectrum for what is deemed necessary by clinical setting or guidelines[6]) is common during the initial stay of patients with severe burns (>20% of full thickness burned surface). These patients usually stay for one day for each per cent deep burn and usually receive antibiotics for up to half of the time spent in hospital.[7]

Prophylaxis before surgery on contaminated skin reduces infection rates in surgical wounds.[8] However, prolonged prophylaxis beyond 24 hours,[8] inadequate doses,[9] or inappropriate regimens[10] promote a vicious cycle that enables more resistant micro-organisms to grow. Current guidelines for using antibiotic prophylaxis in severely burned patients are not evidence based and largely rely on expert opinion, so the systematic review and meta-analysis by Avni and colleagues is important.[1] In contrast to guidelines, the results suggest that systematic antibiotic prophylaxis reduces all cause mortality by 50% (risk ratio 0.54, 95% confidence interval 0.34 to 0.87; five trials).

Although at first glance the results seem impressive, they should be considered with caution because the level of evidence is weak. The data span more than 40 years, with a wide range of micro-organisms and susceptibilities. Meticillin resistant *S aureus* and vancomycin resistant enterococci, now endemic, were unknown 40 years ago. The authors included studies comparing different types of prophylaxis—systemic intravenous, topical, and inhaled antibiotics, as well as enterally non-absorbed and absorbed antibiotics. The duration of interventions ranged from one to 14 days (or until wound healing). The overall quality of the trials was poor, and only five of 17 studies were included in the meta-analysis. Among the five included studies, three were performed in the 1980s and three used oral antibiotics, so that plasma concentrations were unpredictable.

The reduction in mortality relies on a single study in which the patients were literally flooded with antibiotics.[10] The 107 patients included (who had a mean of 19% full thickness burns) received a triple intervention including a systemic third generation cephalosporin for four days, oropharyngeal paste, and selective digestive decontamination with non-absorbable drugs (polymyxin, tobramycin, and amphotericin) until recovery. A significant reduction in mortality and early pneumonia was seen, but no significant difference in wound infection and an increase in late infection and bacterial resistance. Selective digestive decontamination is controversial, and its use remains unclear, because it has been shown to work only in settings with a very low incidence of resistant micro-organisms.

Avni and colleagues concluded that there is a discrepancy between current guidelines, which recommend antibiotic prophylaxis, and their own analysis, which found a reduction in all cause mortality. They consequently call for a large multicentre randomised controlled trial, but this may be difficult to conduct for several reasons. Firstly, the incidence of severe burns is low (10-40 per million inhabitants per year) with variable local microbiological ecology, so generalising the results to clinical practice across centres and continents will be difficult.

Secondly, the outcome will need to be stratified by age, per cent of full thickness burn, inhalation injuries,[11] and surgical strategy, which would make the required number of participants even higher. Thirdly, in the absence of consensus on what defines infection in burn wounds, secondary end points will be difficult to specify. Fourthly, Avni and colleagues showed a threefold increase in resistant organisms after prophylaxis. Accordingly, people in the intervention group may expose controls in the same unit to infection with resistant micro-organisms. Finally, the effect of prophylaxis should be evaluated over a long period of time. Prophylaxis used on admission may reduce the incidence of infection in the short term, but some patients may stay for weeks or months. The development of resistance to antibiotics that are used for prophylaxis may limit the possibility of using them for documented infections.

Unlike other treatments, antibiotics have collateral effects on other patients and the ecosystem of the intensive care unit.[12] This is important in burn centres, where patients are exposed to prolonged and repeated courses of antimicrobials. While more evidence is awaited, we advise caution in using antibiotics and recommend that their use in severely burnt patients should be restricted.

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Acute asthma in children of school age

Parent initiated prednisolone is beneficial but the effect is small

RESEARCH, p 518

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Asthma is one of the most common chronic diseases in childhood. Despite improvements in management it is still responsible for around 32 000 hospital admissions and 40 deaths annually in children in the United Kingdom.[1] Evidence for the effectiveness of guided self management in improving treatment outcomes is extensive,[2] but the contribution of the various components of asthma self management programmes is less clear. Parent initiated treatment of exacerbations with prednisolone is often included in self management plans for children, but evidence for this treatment has been inferred from the confirmed effectiveness of oral corticosteroids in children admitted to hospital with asthma.[3]

In the linked randomised controlled trial, Vuillermin and colleagues assess this strategy in children of school age and find that prednisolone produces small but definite improvements in symptom scores, reductions in health service usage (number needed to treat 7), and a possible reduction in hospital admissions (NNT 25 with a wide confidence interval).[4] So prednisolone helps, but the effect size in this population was small and has to be balanced against the possible harms of repeated courses of oral corticosteroids. The need for the study was highlighted in a systematic review conducted by some of the authors.[5]

Strengths of the study include its single centre population based approach (which meant that about 60% of all eligible children in the area were included in the trial), randomisation by episode rather than by patient, a high degree of ascertainment of symptom scores and other outcomes, and monitoring of adherence by rate of use of the study drug. Interpretation of the findings depends importantly on a clear characterisation of the trial population: these were school age children with four or more episodes of acute wheezing (needing more than 24 hours of increased bronchodilator treatment) in the previous year. They had their eligibility confirmed, their ongoing management optimised, and their self management plan explained by a single paediatrician, the lead author of the study. Their self management instructions for exacerbations included using up to 1200 µg (12 puffs) of salbutamol at a time for acute wheezing, but also not increasing the dosage of inhaled steroid. These children's asthma was probably being looked after to a very high standard, and it would be interesting to know the overall rate of hospital admission for acute wheezing in this population. It would also have been useful to compare illness severity and duration of admission in the six children in the prednisolone group and the 12 children in the placebo group who were admitted to hospital. The study drug was converted on admission to known oral prednisolone in 19% of episodes treated with study prednisolone and 35% of episodes treated with placebo. Thus, two thirds of the episodes of exacerbation in the placebo group avoided any treatment with oral prednisolone.

What are the implications of this study for clinicians responsible for treating and educating school age children with asthma and their carers? Oral prednisolone clearly has a place in the parent initiated management of exacerbations of asthma, but the benefits of this strategy seem to be modest in children whose asthma management is otherwise optimised. The study also shows that in well managed children advice to use up to 12 puffs of salbutamol at a time for acute wheeze seemed to be safe in a series of exacerbations of which a third were treated without the use of systemic steroids; this

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is important because many doctors are still reluctant to give this advice.

A placebo controlled trial in which the leukotriene receptor antagonist montelukast was used in parental management of acute childhood wheezing in subjects aged 2-14 showed similar benefits to those seen with prednisolone in this study,[6] but the use of montelukast did not significantly reduce the use of prednisolone, and monteluklast and prednisolone have not been directly compared head to head. The use of combination inhalers of formoterol and budesonide in temporary higher dosage is another possible strategy for the self management of asthma exacerbations.[7] This option is now recognised in the British asthma guidelines,[8] but most children who develop asthma exacerbations and come to emergency medical attention do not routinely use or need such inhalers.

The present study does not apply to preschool children, who account for most hospital admissions with acute wheezing, and in whom evidence for the effectiveness of prednisolone is weak.[9] Previous negative trials of parent initiated prednisolone—cited in Vuillermin and colleagues' study—were in groups wholly or largely consisting of preschool children. The study does not tell us about the benefits of patient initiated prednisolone in school age children whose management is otherwise poor and in whom the availability of oral corticosteroids for the management of exacerbations might confer greater advantage. It also cannot tell us about the possible contribution of high dose inhaled steroids to parent initiated management of exacerbations. It is to be expected that the dosage of inhaled corticosteroids would need to be substantially increased, as with β agonists, and not just doubled, for them to be effective during asthma exacerbations. Some evidence exists for the effectiveness of this strategy in hospital settings.[10] In severe exacerbations, evidence suggests that prednisolone is more effective than high dose inhaled steroids.[11] However, use of high dose inhaled corticosteroids rather than prednisolone in the context of parent initiated management might reduce the total steroid dose received by children who have repeated asthma exacerbations. The results of this study add to the evidence that trials of high dose inhaled steroid versus oral prednisolone in parent initiated management of asthma exacerbations can be safely and ethically conducted.

Whatever management strategies we advise, careful clinical review after exacerbations, with monitoring of drug usage and possible reasons for the exacerbation, remains a vital component of good asthma care.

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Chronic fatigue syndrome and human retrovirus XMRV

Three studies now refute the original study reporting the link

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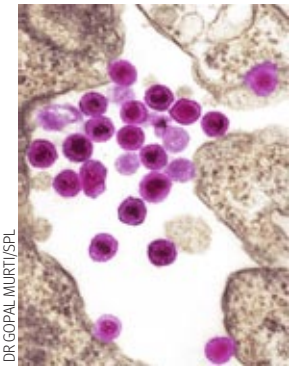
In the linked case-control study, van Kuppeveld and colleagues describe their failure to find evidence of a new human retrovirus in Dutch patients with chronic fatigue syndrome.[1] The study is the latest contribution to a controversy that has surrounded two conflicting publications on the retroviral aetiology of this syndrome.[2 3]

The saga started with an enzyme (RNaseL) that plays a pivotal role in antiviral defences when activated by the interferon released in response to infection. Variants of the gene encoding this enzyme have been linked to an increased susceptibility to prostate cancer, and this led to the identification of a new virus in prostate tissue that was related to, but different from, known xenotropic murine leukaemia viruses[4]; hence the designation xenotropic murine leukaemia virus-related virus (XMRV). Sequence analyses showed that it is not an endogenous human virus, and the fact that eight clones derived from eight different patients are slightly different from one another confirms it as a new virus that has found its way into a human population.

Abnormalities in the RNaseL gene of patients with chronic fatigue syndrome had been reported in some studies,[5] but not in others.[6] Nevertheless, this prompted the search for evidence of XMRV in patients with chronic fatigue syndrome. The resulting study claimed that 67% of patients with chronic fatigue syndrome were XMRV carriers, compared with 3.7% of healthy controls.[2]

The news was received philosophically by most retrovirologists, who are used to claims of associations between retroviruses and diseases that fail to withstand the test of time. Most researchers into chronic fatigue syndrome were also sceptical, mindful of the problems of defining the syndrome, its imprecise boundaries, and almost certain heterogeneity. It was not that they doubted a viral cause in some patients because this had already been shown,[7 8] but the possibility that any single agent or risk factor could account for more than two thirds of cases seemed implausible.[9]

For people with the syndrome, these findings, if true, would have transformed the understanding of the illness and opened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up new avenues of treatment. Some saw this as a definitive response not only to those few professionals who, they claim, continue to doubt the reality of the syndrome, but also to the larger number of professionals who believe that, irrespective of causation, rehabilitative treatments can reduce symptoms and disability. It is depressing that the first, untenable, view is too often confused with the second, a perspective that offers hope to patients and is backed by evidence.

However, as with any discovery, the data must be unequivocal, and the finding has to be confirmed by others. In January 2010, our own group found no evidence of XMRV in a well characterised cohort of 186 patients with chronic fatigue syndrome in the United Kingdom.[3] Van Kuppeveld and colleagues' study adds to this negative evidence. Although the study is small, the patients are well defined and matched in age, sex, and geographical location. The polymerase chain reaction used to amplify XMRV gene sequences has been well controlled and its sensitivity is sufficient to detect low virus copy numbers. XMRV was not detected in this Dutch cohort, a result that comes in the wake of a third study published this month,[10] which also failed to identify XMRV in 170 patients with chronic fatigue syndrome.

The fact that the four studies used different protocols is irrelevant because amplification is controlled by inclusion of a "housekeeping gene"—to show that a known human gene can be amplified under the conditions used—and the sensitivity of the assay is known, as was the case in all three European studies.

Meanwhile, a different strategy is also being considered to reconcile these different findings: that new blood samples should be taken from patients with diagnosed chronic fatigue syndrome and sent to laboratories capable of carrying out the analysis. This is likely to happen.

Three studies have now generated data that are in stark contrast to those of the original study. However, at least two explanations for this are still possible. The first, and more unlikely, explanation is that XMRV infection is geographically confined to the United States. The second is that the virus is infecting an atypical cohort. This may well be so. Although the patients were not well described in the original study, van Kuppeveld and colleagues provide the additional information reported at a conference last year that the patients in question came from an outbreak of chronic fatigue syndrome at Incline village on the northern border of Lake Tahoe in the mid-1980s. Whether or not this was a genuine cluster was never established,[11] but an association with viruses, such as Epstein-Barr virus and human herpesvirus 6, has already been suggested.[12] It is possible that XMRV is implicated in the Lake Tahoe episode but does not play a substantial role in most cases of chronic fatigue syndrome elsewhere.

The results from other US laboratories investigating XMRV and chronic fatigue syndrome are eagerly awaited. If the link fails to hold up, it will be another bitter disappointment to affected patients although XMRV may turn out to be important in the pathogenesis of other diseases.

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Use of full body scanners at airports

Medical risk is negligible, but concerns about privacy remain

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Doctors on doc2doc, BMJ Group's online global clinical community, are discussing the use of full body scanners at airports. To have your say in the discussion, visit http://tinyurl.com/ygyp9eb

Since the attempted bombing of an aeroplane bound for the United States on Christmas Day 2009, several countries have made or are in the process of making a decision about mandatory use of full body scanners at airports. "Full body scanners" or "whole body scanners" can be classified as either "millimetre radio wave" or "backscatter" technologies.

Millimetre radio wave systems scan travellers by bombarding them with radio waves and collecting the reflected radio waves via antennae to generate an image.[1] This technology does not use x rays. In contrast, backscatter systems use low intensity x rays to scan the body. The x rays do not penetrate the body but bounce off the skin, and are then captured by detectors to create images. These x rays are useful for detecting objects hidden under clothing and taped on the skin but not for detecting objects hidden inside the body.[2] For this, transmission x ray systems are needed.[2] The table lists the doses of radiation produced by backscatter systems and the number of backscatter scans needed to yield an equivalent dose to that of a chest x ray and other radiation sources.[3-8]

A typical backscatter scan takes about eight to 15 seconds to perform and provides two images—front and back.[2] For the past few years, full body scanners have been in use as secondary screening devices at various airports, including Heathrow Airport in London, and travellers have been allowed to opt out.

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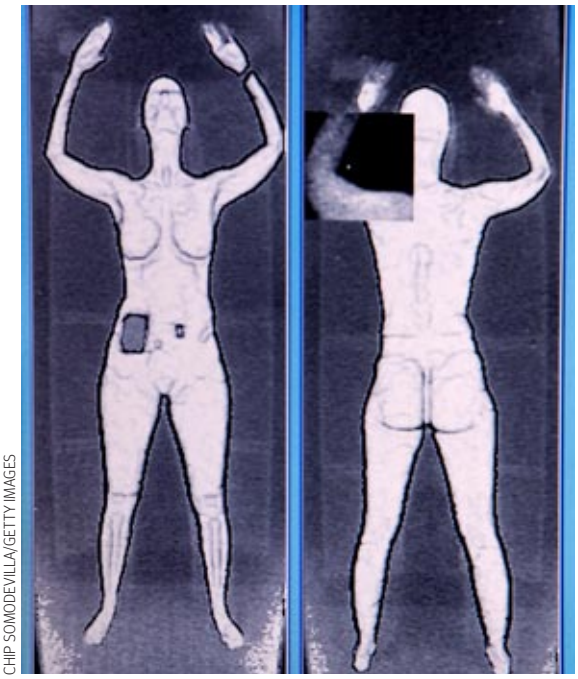
With increased emphasis on airport security, however, mandatory screening of travellers with full body scanners may soon become routine.

Several important concerns exist regarding full body scanners—biological risks to travellers and concerns about privacy, the longevity of images, and the stability of scanners. In this context, it is recommended that radiation doses from backscatter systems should not exceed 0.1 µSv, and the doses measured have been reported to be between 0.05 µSv and 0.1 µSv per scan.[2 3]

A person would therefore have to undergo 1000-2000 backscatter scans before receiving a dose equivalent to a medical chest x ray (100 µSv).[4] The dose of radiation from a single backscatter scan is equivalent to that received from less than 30 minutes of background radiation and two to 10 minutes of average air travel.[5 6 9]

The National Council of Radiation Protection and Measurements (NCRP), an advisory body to the United States government, uses the concept of "negligible individual dose (NID)," which is, "an effective dose corresponding to the level of average annual excess risk of fatal health effects attributable to radiation exposure below which effort to further reduce the exposure to an individual is not warranted." NID is set at an annual effective dose of 10 µSv per source or practice.[7] A person would have to undergo 100-200 backscatter scans before receiving a dose equivalent to NID.



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Radiation doses from backscatter systems and number of backscatter scans equivalent to doses from various sources of radiation

Source	Dose or dose equivalent
Backscatter scan (µSv/scan)	0.05-0.1
No of scans equivalent to typical chest x ray dose (100 µSv)[4]	1000-2000
No of scans equivalent to annual dose limit for public from a single source (~250 µSv)[9]	2500-5000
No of scans equivalent to one day of natural background radiation (10 µSv/day)*	100-200
No of scans equivalent to NID† dose	100-200
No of scans equivalent to average dose from air travel (4 µSv/h)[7]	40-80

*Annual natural background radiation ~3100 µSv[5] or ~2400 µSv[6].

†NID=negligible individual dose (~10 µSv)[8].

The Nuclear Regulatory Commission in the United States recommends an annual limit on doses to the public of 1000 µSv, and 250 µSv a year from any single source or practice.[8] To exceed 250 µSv a year at a dose of 0.1 or 0.05 µSv per scan, a traveller would need to have 2500-5000 scans, which is highly unlikely in one year.

Another concern about backscatter systems is the ability of scanners to deliver a low radiation dose but yield images of sufficient quality. This is especially pertinent in countries where poor or non-existent infrastructure means that periodic checks are not guaranteed. It is therefore essential to establish routine maintenance and quality assurance programmes and involve trained professionals, such as health physicists or medical physicists, to verify the radiation dose delivered by the backscatter systems.[10 11] Even though the radiation exposure to operators is negligible, they should undergo radiation safety training to avoid any inadvertent exposure to radiation.[2 10 11]

The term "virtual strip search" has arisen because detailed images may infringe personal privacy but concerns can be mitigated by having the image viewing stations at remote locations, not next to the scanners, and also by ensuring that images cannot be saved in the long term. Software programs have been developed to modify the backscatter image to make the image appear more like a "chalk outline," with less personal detail. Currently, the use of full body scanners is optional, but when it becomes mandatory, the alternative measures for people who decline to go through these scanners are complete physical pat-downs and other technologies that may be even more intrusive and cumbersome.

Current calculations indicate that backscatter systems are safe for general use, even in infants and children, pregnant woman, and people with genetically based hypersensitivity to radiation. When considered in the context of a potential increase in security, the benefits outweigh the potential for harm.

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The first draft of DSM-V

If accepted, will fan the flames of false positive diagnoses

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The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), published by the American Psychiatric Association, is the official method for making psychiatric diagnoses in the United States. It is also widely used around the world, particularly for research purposes. The current edition, DSM-IV, was published in 1994. The first draft of the next revision, DSM-V, was recently posted on the internet (www.dsm5.org) and was accompanied by considerable press fanfare and professional controversy.[1]

DSM-V has been in preparation for three years and is scheduled to appear in 2013. The work on DSM-V began with the unrealistic ambition of producing a paradigm shift in psychiatric diagnosis. The working groups preparing the various sections were encouraged to be innovative and to think "out of the box."[2] The criteria for making changes and the requirements were specified only recently and are fairly fluid.[3] The whole process has also been criticised for being secretive, closed to external influences, and disorganised.[4-6]

The experience with DSM-IV should offer a painful lesson and caution. Efforts were made to be conservative and rigorous.[7] Nonetheless, DSM-IV was an unwitting contributor to three false positive "epidemics." Its publication coincided with high rates of attention deficit hyperactivity disorder, autistic disorder, and childhood bipolar disorders.[8] Other factors contributed to these epidemics, particularly the ubiquitous marketing efforts of drug companies directed at doctors and the general public.

The lesson is clear: once the diagnostic system is in general use, even small changes can be amplified and twisted, with harmful and unintended consequences. The proposals contained in the first draft of DSM-V could potentially set off at least eight new false positive epidemics of psychiatric disorder. In their efforts to innovate, the working groups could expand the territory of mental disorder and thin the ranks of the normal. Five proposed new diagnoses are defined by non-specific symptoms that are common in the general population—binge eating, mixed anxiety depression, minor neurocognitive problem, risk of psychosis, and temper dysregulation. Three existing disorders would have a major lowering of their already overinclusive diagnostic thresholds: attention deficit hyperactivity disorder, bipolar disorder, and major depressive disorder.

The changes suggested for DSM-V are well meaning. They are intended to promote the early identification and treatment of mental disorders and reduce resistance to treatment. The problem is that every increase in the sensitivity of a psychiatric diagnosis is accompanied by a concomitant drop in its specificity. False negatives can be reduced only at the cost of producing many more false positives. Because the suggested changes all occur at the boundary between mental disorder and normality, they could create vast numbers of misdiagnosed new "patients."

The consequences are grave. For individuals, these include unnecessary treatment with drugs that have unproved benefit but known harm (particularly weight gain); stigma; difficulties getting life insurance and disability insurance; and a reduced sense of personal responsibility and control. For society there is the expense of unnecessary treatment; the diversion of scarce resources away from people who need it to those who essentially don't; and a reduction in morale and resiliency, as the usual problems of everyday life become medicalised into mental disorders.

Early identification and intervention require that a specific diagnostic test (with a low false positive rate) and an effective and safe treatment is available. The suggestions for DSM-V would offer the worst of all possible worlds. They would cast so wide a net as to guarantee a harvest of false positives. The efficacy of the corresponding treatments has not been proved, and their safety—especially the atypical antipsychotics, which can cause weight gain—is in doubt.[9]

Two hundred years ago, Pinel defined the domain of psychiatry with the first systematic classification of its disorders. Every new system since has progressively expanded its boundaries. Old disorders are almost never discarded; yet new disorders and lowered thresholds have taken ever bigger bites out of normality. Who is responsible? Psychiatric classifications are inevitably created by experts. Experts dread false negatives yet can be blind to the problems of false positives. It must be appreciated that disorders originating and studied in highly selected research environments take on a life of their own when transplanted to primary care and nurtured by drug company promotions. The enthusiasms of experts should always be contained by a careful risk-benefit analysis that includes a critical review of the scientific literature, field testing in primary care settings, and a consideration of all the potential unintended consequences. Such analyses would probably sink the prospects of all the false positive diagnoses that are suggested for DSM-V and thus spare us from having yet another round of costly and dangerous iatrogenic epidemics.

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