Venlafaxine for major depression

More evidence that risks outweigh benefits for most patients?

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In this week's *BMJ* Rubino and colleagues provide new evidence that informs the debate about whether antidepressants increase the risk of suicide.[1] The study, a retrospective observational analysis of the General Practice Research Database, found that patients prescribed venlafaxine were more likely to attempt or complete suicide than patients prescribed citalopram, fluoxetine, or dothiepin. Adjustment for possible confounders, however, greatly reduced the excess risk.

Venlafaxine is a serotoninergic and noradrenergic reuptake inhibitor, and it may be more effective than selective serotonin inhibitors for major depression.[2 3] However, patients often discontinue treatment because of side effects.[4]

The database analysed is the world's largest computerised database of anonymised longitudinal medical records from primary care (more than 3.4 million active patients, about 13 million in total since 1987, from around 450 primary care practices throughout the United Kingdom; www.gprd.com). The database has been used extensively for pharmacoepidemiological research, including previous studies examining the possible association between death from suicide and the use of antidepressant drugs.[5 6]

The non-experimental nature of the database creates methodological problems that can make results difficult to interpret, as the study by Rubino and colleagues shows. Firstly, the patients treated with venlafaxine were probably selected clinically, and differed from those treated with other agents in several variables related to the risk for suicide. Although sophisticated statistical analyses were used to control for potential confounding, some variables—such as diagnosis, comorbidities, and pre-existing depression or suicidal ideation—may not have been effectively accounted for. Moreover, there may have been residual confounding by uncontrolled variables, such as treatment dosages and adherence to treatment.

Secondly, the choice of the primary outcome is important. Although some epidemiological studies have used the outcome of all deliberate self harm, Rubino and colleagues restricted the primary outcome to acts with a deliberate suicidal intent. Deliberate self harm, particularly suicide, is often thought to be a relatively "hard" outcome in studies of antidepressants, but enormous scope exists for ascertainment bias. For this reason, in a meta-analysis of randomised clinical trials of long term lithium therapy, we used all cause mortality as the primary outcome, and suicide and deliberate self harm as secondary outcomes, to limit ascertainment bias and make the findings more robust.[7]

Thirdly, differences in the drug being compared and sample populations may explain heterogeneity between the results of different observational analyses.[5 8] For example, Rubino and colleagues selected only specific antidepressants as comparators (citalopram, fluoxetine, and dothiepin), excluded other agents, and did not include a reference group of patients not taking antidepressants.

Observational evidence offers insights into long term and real world outcomes for large groups of people, but it can rarely show a convincing causal relation between two events. It can be hypothesised that the drug itself can precipitate suicide, because of its potential mechanism of action. Randomised controlled trials are better able to establish causal relations, but they usually follow highly selected samples of patients for short periods.[9] Systematic reviews of randomised controlled trials may increase statistical power, but absolute numbers of patients having rare adverse events such as completed or attempted suicide are low. Thus, reporting or not reporting a few cases can completely change the overall outcome.[10] Even with these limitations, systematic reviews have consistently reported an excess risk of suicide in children and adolescents with major depression taking antidepressants, but not in adult patients.[11 12]

Despite these uncertainties, clinically useful conclusions for everyday clinical practice need to be formulated. Currently, UK guidelines recommend that treatment with venlafaxine should be started or managed only under the supervision of specialist mental health medical practitioners. The Medicines and Healthcare Products Regulatory Agency has recently changed this guidance, however, to apply only to severely depressed patients or those in hospital who need doses of 300 mg daily.

Recent observational evidence indicates that, in suicidal patients who have ever used antidepressants, current use of any antidepressant is associated with an increased risk of attempted suicide and with a decreased risk of completed suicide and death.[8] In this analysis, venlafaxine was associated with the highest risk of suicide.[8] A similar risk profile for venlafaxine was highlighted by reanalyses of data from clinical trials conducted in children.[11] Finally, the Food and Drug Administration in the United States, the Medicines and Healthcare Products Regulatory Agency, and the manufacturer of venlafaxine have issued a warning about the risk of cardiotoxicity and toxicity associated with overdose of venlafaxine.

Venlafaxine therefore has a consistent but unexplained risk of increased suicide and toxicity. Despite evidence of its marginally greater efficacy compared with other antidepressants,[2 3] current evidence suggests that venlafaxine should not be first line treatment for people with major depression.

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Childhood intelligence and being a vegetarian

Do bright children grow up to make healthy choices?

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Evidence increasingly suggests that intelligence is associated with health and survival,[1 2 3] although the reasons for this are not fully understood. To varying degrees, intelligence could mediate the long term impact of early adverse circumstances (such as overcrowding), influence the acquisition of factors that protect health, and reflect underlying biological mechanisms that regulate health. A cohort study in this week's *BMJ* by Gale and colleagues[4] assesses whether intelligence can influence the acquisition of protective factors. In a large representative population study of more than 8000 British men and women, intelligence in childhood was associated with a vegetarian diet in mid-adulthood, and this was independent of educational attainment and social class.[4]

So what do the results say about the relation between intelligence and personal values, and whether intelligence influences lifestyle choices that protect health? An analysis of five prospective studies found that vegetarians had a mortality rate 76% lower than that of non-vegetarians, after adjusting for age, sex, and smoking.[5] A randomised controlled trial found that higher intakes of vegetables, legumes, fruit, and bread (as well as more fish and chicken instead of red meat) were associated with reduced total mortality, death from heart disease, and incident cancer in men who had survived myocardial infarction.[6]

Like all good research, the study by Gale and colleagues raises provocative but testable questions. Firstly, given that childhood cognition is itself modified by nutrients, including iodine, iron, zinc, vitamin B-12, folate, and omega 3 fatty acids,[7] do dietary patterns established in childhood influence food choice in adults? If so, might this long term influence in part explain the association between intelligence and vegetarianism? Little is known about how diet in childhood relates to that in adulthood, although preliminary evidence from the 1946 British birth cohort suggests that people from families who ate large amounts of fruit in childhood continued to do so in midlife, whereas those from families who ate little fruit in childhood also had low fruit consumption in midlife.[8]

Secondly, observational studies have reported positive associations between the intake of nutrients such as B complex vitamins, omega 3 fatty acids, and unsaturated unhydrogenated fats in adults and cognitive function in later life,[9 10 11] although a randomised controlled trial found no effect of long term vitamin E supplementation in healthy women aged 65 years or more.[12] Might the associations with cognitive ageing reported in observational studies be explained to some extent by people choosing their dietary habits according to prior cognitive ability?

So to return to where we began, does diet mediate associations between childhood intelligence and adult health, as Gale and colleagues ask? Significant mediation of this kind was found in relation to obesity in the British 1958 birth cohort, whereby a high healthy diet score—based on consumption of fried food and fresh fruit at age 33—along with educational attainment significantly accounted for the association between childhood intelligence and weight gain between 16 and 42 years.[13] If diet does mediate (or at least partly mediate) the effect of intelligence on other health outcomes—such as cardiovascular disease, colorectal cancer, diabetes, and Alzheimer's disease—then public health interventions to encourage eating a consistently healthy diet may be beneficial. Such an approach should begin with parents encouraging children to eat healthily, with the aim that they continue to make

healthy food choices as adults, while simultaneously teaching adults themselves about healthy food choices and how these choices may have developed during childhood.

While Gale and colleagues found that intelligence is associated with food choice independently of educational attainment, it is also important to know if education is associated with food choice independently of intelligence and, if so, in what way. If schools make an important contribution to the development of healthy food choices, then it may be best if parents and teachers provide consistent advice on these choices.

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Leprosy after starting antiretroviral treatment

An increasingly reported clinical problem but not a serious public health risk

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Recent media reports have highlighted a "startling and worrisome new link" between antiretroviral treatment and leprosy.[1] Some people infected with HIV who have started such treatment in countries where leprosy is endemic have developed florid leprosy lesions in the initial months of treatment. What underlies these unusual manifestations and do they have implications for the control of leprosy?

The note of alarm is understandable—leprosy and HIV are both greatly feared diseases. The manifestations described, however, are a well recognised complication of antiretroviral treatment known as immune reconstitution disease or immune reconstitution inflammatory syndrome (IRIS).[2] This presents with the manifestation (or "unmasking") of a previously subclinical coinfection or the deterioration of an opportunistic infection that had been responding to treatment. These effects are due to antiretroviral treatment causing the rapid recovery of cell mediated immune responses, which trigger host immune responses to foreign antigen. Such reactions typically occur during the first four months of treatment—the most rapid phase of immune recovery.

The HIV pandemic has had surprisingly little effect on the epidemiology and clinical features of leprosy.[3] However, immune reconstitution disease is a new and unexpected clinical interaction between these diseases in patients who have just started treatment. The first published case of leprosy associated immune reconstitution disease occurred in 2003 in a Ugandan living in London.[4] More cases have been described since, mostly in patients living in South America.[3 5 6] In most cases, immune reconstitution disease triggered the initial presentation of leprosy, often with a reactional state—acute inflammation within the leprosy lesions that may result in rapid loss of nerve function. Some reactions have been unusually severe with skin ulceration, protracted cutaneous inflammation, and neuropathy.[3-6]

Antiretroviral treatment has been available since 1996 in countries with high average incomes. Immune reconstitution disease has been well characterised in this setting and is associated with a predictable range of opportunistic infections.[2] Antiretroviral treatment is increasingly being used in resource poor countries where different coinfections exist; which of these infections have the potential to be associated with immune reconstitution disease is not yet clear. Immune reconstitution disease has, for example, recently been described in association with the parasitic infections leishmaniasis, strongyloidiasis, and schistosomiasis.[7] Many of these cases were in immigrants receiving antiretroviral treatment in countries with higher incomes. Leprosy has joined this growing list of tropical infections associated with immune reconstitution disease.[4-7]

Antiretroviral treatment is now more accessible in resource poor countries where leprosy is still endemic, such as South America, India, and Africa; not surprisingly, reports of leprosy associated with immune reconstitution disease are increasing.[1] This disease is most likely to be seen in India, where the HIV epidemic is growing and where 161 457 new cases of leprosy were diagnosed in 2005 alone.[8] From the patient's perspective, HIV infection and leprosy are both highly stigmatising diseases, and having both is understandably distressing. This distress may be heightened by the patient's perception that the leprosy was caused by

the antiretroviral drugs. Frequent cases of this disease could make patients less enthusiastic about antiretroviral treatment programmes. Importantly, some lesions seen in leprosy associated with immune reconstitution disease are unusually florid, and severe neuropathy triggered during antiretroviral treatment might lead to permanent disability.

Medical staff who provide antiretroviral treatment to patients in (or originating from) countries where leprosy is endemic need to be aware that leprosy may present as immune reconstitution disease. The diagnosis of leprosy is often missed or delayed in immunocompetent people, and the likelihood of diagnostic confusion and delay is even greater in patients infected with HIV who start antiretroviral treatment. Immune reconstitution disease should be considered in patients who present during the initial months of antiretroviral treatment with erythematous and oedematous skin lesions or loss of peripheral nerve function (as shown by anaesthesia or muscle weakness). Missed or delayed diagnoses may lead to the development of permanent disability.

The clinical spectrum of manifestations needs to be defined, and surveillance is needed to determine the frequency of leprosy associated with immune reconstitution disease. A key question is how best to manage reactional states triggered by antiretroviral treatment because immunosuppressant therapy in patients with HIV may have greater risks than in patients without HIV. Prolonged and robust immunosuppressive therapy may nevertheless be necessary in some cases.[4]

From a public health perspective, we have less cause for alarm. Leprosy presenting as immune reconstitution disease represents the manifestation of previously subclinical disease and not the development of new infections. Increased numbers of leprosy diagnoses due to immune reconstitution disease therefore do not indicate a deterioration in leprosy control. Moreover, such disease usually manifests itself with the non-infectious borderline forms of the disease.[3] These cases are unlikely to pose a risk of infection to people in antiretroviral treatment clinics or in the community. Furthermore, whereas immune reconstitution disease associated with tuberculosis or cryptococcal meningitis has an appreciable risk of mortality,[9,10] disease associated with leprosy is not life threatening.

These facts need to be put into perspective. Immune reconstitution disease associated with leprosy has been reported in a relatively small, albeit increasing, number of patients. Meanwhile, it is estimated that in 2005 alone between 250 000 and 350 000 deaths were prevented by antiretroviral treatment in low and middle income countries.[11] Antiretroviral treatment will continue to save hundreds of thousands of lives each year, but unusual manifestations of immune recovery including leprosy will inevitably occur.

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Emergency care in the first 48 hours

"Acute physicians" herald the new specialty of acute medicine

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The importance of the first 48 hours in producing successful outcomes for acutely ill patients cannot be underestimated. The definition of a successful outcome depends on who is measuring it. Clinicians look for successful diagnosis and treatment, governance directors look for safety and use of pathways and guidelines, educators look for training opportunities, managers want to decrease length of stay, whereas patients (usually) just want to get better and go home. The problem is how to deliver on all of these fronts.[1]

The traditional model of delivering acute care for medical patients, who make up the bulk of acute admissions to hospital, has been slowly changing. The older model of a hierarchal medical team has begun to disappear.[2] There have been many drivers to this change. In the United Kingdom changing patterns in the availability of junior doctors (such as the European Working Time Directive and the Modernising Medical Careers project (www.mmc.nhs.uk/pages/home)) has led to team fragmentation and multiple handovers of acutely ill patients.[3] A growing deficit of primary care after normal working hours has meant an increase in hospital admissions at night. The imposition of a maximum stay of four hours in emergency departments in the UK has meant that many acutely ill medical patients have been rapidly moved to medical wards, perhaps before a full assessment.[4]

Some emergency departments have responded to the challenge by providing some acute inpatient care for up to 24-48 hours, but this is far from widespread.[5]

Specialty physicians are becoming less keen to participate in the acute medical take roster, which can lead to less input from consultants regarding the initial assessment and care of inpatients.[3] This problem is much greater in Australia, where the specialty of internal medicine is facing an increasing shortage of recruits, as increasing numbers of trainees opt for the more remunerative procedural specialties (which provide invasive procedures such as endoscopy, angiography, and bronchoscopy).[6] The increasing dearth of general physicians means that some hospitals have no general medical teams. In such hospitals, patients with several chronic diseases can no longer be treated by one team alone and require multiple consultations and longer stays in hospital.[7]

In the United States the rising role of the hospitalist, who is based entirely in the hospital and provides acute medical care, conflicts with the traditional role of the patient's primary care doctor, who previously visited the hospital to provide inpatient care. The hospitalist model is becoming the benchmark for acute care for many medical patients in hospital in the US, although these clinicians are not recognised as internal medicine physicians in most places.[8]

The UK has seen the rise of the "acute physician," who is dedicated to managing the first few days of all acute medical admissions. These individuals come mainly from the specialty of general medicine, but as the acute physician specialty develops its training model and approval for core training, it will soon have its own specialists.[4] Individuals with core training in emergency medicine or critical care medicine will also join, so that a specialty dedicated to acute medical care will grow.[9]

Soon the Joint Committee on Higher Medical Training will implement the model for two years of common stem training in acute care to follow on from the two foundation years that new UK graduates now work. Thus, six months each of intensive care, emergency medicine, anaesthesia, and acute medicine will provide the robust platform for specialty training in acute medicine.

The question is whether this acute physician model is useful. Has it evolved only out of political change, or can it really make a difference? The expectation of the Royal College of Physicians is that with dedicated acute physicians undertaking ward rounds twice daily, seven days a week, the model should work.[10] Acute physicians will initiate investigations and interventions from the moment the patient arrives in the emergency department or acute assessment unit. This will enable rapid assessment and management of patients with potentially complex comorbidities and multisystem disease from the outset. Acute physicians will coordinate allied health interventions and plan discharge from the outset. They will also liaise with specialist inpatient teams and where possible with domiciliary services and "hospital in the home" teams to avoid treating patients in hospital when they could be treated at home. The evidence to date on the effectiveness of the model is piecemeal. Better short term outcomes have been reported with the acute physician model than with traditional team based care in the UK, and the US hospitalist model has shown cost efficiencies without any robust long term outcome data as yet.[11]

The challenges are obvious if acute physicians are to succeed. The political drivers for change are strong, and hospital executives and commissioners will always favour a service that can deliver safe, effective, efficient, and fast care for inpatients. But what of the specialty of acute medicine itself? Respect from peers is hard to earn, and generalists are not so highly regarded as the superspecialist who may be seen (by colleagues and patients) as the master of a specific craft or skill set. To paraphrase Dame Carol Black (the last president of the Royal College of Physicians and an important figure in the development of this specialty) speaking at a meeting of the Society for Acute Medicine held in September 2006 in London: a specialty can exist only when a robust body of published work provides evidence of what the specialty does and why it should continue to exist. Thus will it earn the respect of its peers.

This is an exciting time to be in acute medicine; it should be the core specialty in the hospital of the future, around which other inpatient activity will flow.[12] Acute physicians should be competent to manage medical emergencies and make complex multisystem medical diagnoses. But they should also be able to smooth the path of the increasingly truncated hospital journey. They should be the link between home treatment and brief but focused hospital based treatment, and they should also coordinate other specialist care whenever it is needed.

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Allergy to hair dye

Its incidence is rising, as more and younger people dye their hair

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For more than 100 years para-phenylenediamine (PPD) and other related members of the aromatic amine family have been the main agents used in permanent hair dyes, and more than two thirds of hair dyes currently contain PPD. This compound is an effective hair dye owing to its low molecular weight, its ability to penetrate the hair shaft and follicle, its strong protein binding capacity, and its rapid polymerisation in the presence of a coupler (a kind of catalyst) and an oxidising agent. However these properties also make PPD an ideal contact allergen and, indeed, it is among the most potent.[1]

During the 20th century allergic reactions to PPD became such a serious problem that it was banned from hair dyes in Germany, France, and Sweden.[2] Current European Union legislation allows PPD to comprise up to 6% of the constituents of hair dyes on the consumer market (3% when added to the oxidising solution required to develop the colour). No satisfactory or widely accepted alternatives to the aromatic amine agents are available for use in permanent hair dye.

A patient with contact allergy to a hair dye often presents with dermatitis on the face or around the hair line. Severe reactions also occur; some patients have had such gross facial swelling that they have been treated initially for angio-oedema and some have been admitted to hospital.[3] Contact allergy to PPD and related aromatic amine dyes is detected by patch testing using 1% PPD in petroleum jelly. This is included in most standard series of patch tests used to screen for contact allergy in patients with eczema. Such screening may, however, fail to detect allergic reactions to other hair dyes.[4]

Dermatologists report anecdotally that the frequency of positive reactions to PPD on patch testing is increasing. This was confirmed in a recent retrospective survey in London, with a doubling in frequency over six years to 7.1% in a clinic for adults with contact dermatitis.[5] This rise could not be attributed to an increase in occupational exposure (in hairdressers), medicolegal claims, the use of temporary "henna" tattoos containing high concentrations of PPD (often when on holiday),[6] or a greater proportion of South Asian patients—who tend to have high rates of allergy to hair dye.[7]

In the same London clinic from 1965 to 1975 between five and 11 patients with non-occupational PPD allergy were seen each year.[8] More recently this figure has consistently exceeded 40 such patients annually. This increase is unlikely to be due to more consistent referral and diagnosis because only 15% of people with a history consistent with hair dye allergy seek medical attention, and of these only a minority are tested for allergy to hair dye.[3 9]

Data from patch testing in Belgian and Portuguese centres confirm the pattern seen in London (personal communication by A Goosens to the European and Environmental Contact Dermatitis Research Group in Leuven, 2005), as do studies from Denmark,[9] Germany,[10] and Singapore.[11 12]

In Bangkok screening of 2500 normal adult volunteers by patch testing showed a 2.7% prevalence of PPD allergy which, when extrapolated to the general population, suggests that more than one million Thai adults may be sensitive to PPD,[w1] while in Germany up to 1.3 million adults in the general population may be sensitive.[w2]

Market research indicates that more people are dyeing their hair and are doing so at a younger age. In 1992 a survey by the Japan Soap and Detergent Association of young people in Tokyo, 13% of female high school students, 6% of women in their 20s, and 2% of men in their 20s reported using hair colouring products.[w3] By 2001 the proportions using hair colouring agents had increased in these three groups to 41%, 85%, and 33%, respectively. Furthermore, female high school students and young women were dyeing their hair at shorter intervals. In America the proportion of young men dyeing their hair increased by 25% in the five years after 1998.[w4] One leading Japanese company saw its hair dye sales more than double in the 10 years up to 2001, and according to data from the Japanese government total shipments of hair dye to Japan doubled in the 10 years up to 2001.[w5] In Denmark 75% of women and 18% of men have used hair dye,[9] and the median age for first use of hair dye for both men and women is during the teenage years.[9] Severe hair dye reactions among children have recently been reported.[w6]

Wider debate on the safety and composition of hair dyes is overdue—among medical and scientific communities, the public, and legislators. Cultural and commercial pressures to dye hair and, perhaps, the widespread obsession with the "culture of youth" are putting people at risk and increasing the burden on health services. It may not be easy to reverse these trends, however, as some patients have continued to use such dyes even when advised that they are allergic to them and risk severe reactions.[w7]

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