Tricyclic antidepressants for migraine and tension-type headaches

Largely beneficial, but a lack of research leaves clinical questions unanswered

In the linked meta-analysis, Jackson and colleagues assess the efficacy of tricyclic antidepressants in the treatment of migraine, tension headache, and mixed headache.1

Tricyclic antidepressants have a long history in the treatment of headache. In 1964 Lance and Curran reported a better response to amitriptyline (30-75 mg/day) in chronic tension headache (n=280) compared with 11 other commonly used drugs (such as benzodiazepines, vasodilators, and sedatives).2 They also reported a placebo controlled crossover trial of 27 patients that showed clinically significant improvements (≥50% reduction) in headaches in 55% of patients taking amitriptyline, but only 11% of those taking placebo. When the results for amitriptyline were aggregated across the two studies, the effect of amitriptyline became more pronounced over time, with independent of the presence of depression, was evident in patients with continuous as well as episodic headaches, and was most pronounced in older (≥60 year of age) patients. A decade passed before similar positive findings were reported for migraine.3

With replication of these findings tricyclic antidepressants, particularly amitriptyline, have been recommended in textbooks for at least 35 years. With the advent of formal treatment guidelines for headache, tricyclics also have been recommended in clinical guidelines for the treatment of tension-type headache and migraine.4,4

The current meta-analysis updates the evidence base for tricyclic antidepressants in the treatment of migraine and tension headache.1 Results from the 37 trials of tricyclic antidepressants are analysed; the 20 placebo controlled trials primarily evaluate amitriptyline (14 trials) or clomipramine (four trials). The meta-analysis largely confirms Lance and Curran’s original observations. Across trials, low dose tricyclic antidepressants (mean amitriptyline dose 80 mg/day) reduced headache by at least 50% compared with placebo (tension: relative risk 1.41, 95% confidence interval 1.02 to 1.89; migraine: 1.80, 1.24 to 2.62). The proportion of people who stopped treatment did not differ significantly between people taking tricyclic antidepressants or placebo. Treatment effects increased over time. Other preventive drugs (topiramate or β blockers) showed no advantage over tricyclic antidepressants. Tricyclic antidepressants were significantly more effective than serotonin reuptake inhibitors (tension (four trials): 1.73, 1.34 to 2.22; migraine (five trials): 1.72, 1.15 to 2.55), although dry mouth, drowsiness, and weight gain were also significantly more common with tricyclics.

Conclusions that can be drawn from meta-analyses depend on the number and quality of available trials. As the authors rightly point out, the number of studies was not large and most were small and of short duration (average 11 weeks). Moreover, most trials would not meet current methodological standards because 80% (16/20) of placebo controlled trials were completed at least 20 years ago.7,8 As a result, convincing evidence is available for only the most general conclusion: amitriptyline is more effective than placebo for migraine and tension headache. Amitriptyline also seems to be more effective than serotonin reuptake inhibitors, although few direct comparisons are available.

After a half century of research the most important clinical questions remain unanswered. Is the observed effect of amitriptyline a true class effect of tricyclic antidepressants or specific to a subset of tricyclics? Are newer selective dual action (serotonin and noradrenaline) antidepressants as effective as tricyclic antidepressants with, potentially, a more favourable side effect profile? How does the effectiveness of tricyclic antidepressants compare with other preventive drugs or with non-drug treatments? Which people are the best candidates for tricyclic antidepressants rather than other preventive drugs or non-drug treatments? Can tricyclic antidepressants be beneficially combined with other preventive drugs or non-drug treatments in people who do not respond to monotherapy? Secondary analyses of available clinical trial data can yield answers to some of these questions.9 However, just a few large properly designed trials might answer many of these questions, as well as other clinically relevant questions.

Unfortunately, a 50 year history indicates that such trials will not be conducted. Incentives are too few and disincentives too substantial for the drug industry to

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Promotion of cycling and health

Modest effects in individuals could translate to large population effects

England’s chief medical officer in 2009 called physical activity a potential “wonder drug,” and promoting physical activity has been called a “best buy” in public health. In our sedentary and technologically advanced societies, population levels of physical activity are low, and knowledge about how to invest in this best buy is urgently needed. Our challenge is to find methods of making this wonder drug more palatable to more people more often.

Reviews of physical activity promotion suggest that an increase in everyday walking and cycling could generate a considerable public health gain. The evidence base for how best to promote walking is growing. Cycling is also a relatively simple and effective way for people to gain an adequate “dose” of regular health enhancing physical activity, and many people have access to a bike, but we know little about how to promote this activity.

In the linked systematic review, Yang and colleagues assess the effectiveness of interventions to promote cycling, and whether promoting cycling influences overall levels of physical activity. The review provides a realistic assessment of what can be achieved. The results suggest that both individual and community-wide approaches to promoting cycling are needed to benefit population health but that gains would be modest (increases in the proportion of trips made by bicycle of up to around 3% in population level interventions are cited in the review). However, modest gains spread across the population would have an effect on health. Also, it is not clear whether people who take up cycling reduce other modes of activity, such as structured forms of exercise, but the review suggests this is not the case.

This review highlights several challenges and opportunities regarding the promotion of cycling. Public attitudes and perceptions influence decisions about mode of travel. A systematic review of children’s attitudes to walking and cycling concluded that policies to promote walking and cycling would be more successful if they tackled concerns about safety and promoted the capacity of children and young people to make their own choices about transport. Evidence suggests that reducing speed improves the safety of pedestrians and cyclists. One study found that introducing mandatory 20 mph (32 km an hour) zones in London was associated with a significant reduction in serious casualties among child pedestrians and cyclists.

The World Health Organization’s health economic appraisal tool (www.apho.org.uk/resource/view.aspx?RID=78773) for cycling ascribes a value to the health benefits arising from regular cycling. The tool shows that investment in cycling is highly cost effective, especially in comparison with investment in road building.
Increased levels of cycling as a mode of travel might also improve environmental health by reducing traffic congestion, air pollution, and carbon emissions. The estimated health benefits of cycling have been assessed as being substantially larger than the risks relative to car use, and societal benefits as a result of reduced air pollution and eventually fewer road traffic injuries have been proposed.3

A manifesto produced earlier this year by the Faculty of Public Health and the Royal Society for Public Health has called for a 25% increase in cycle lanes and cycle racks and a 20 mph speed limit in built up areas.10 Yang and colleagues’ review provides further evidence to support this prioritisation and their conclusions provide a strong argument that better measurement of the impacts of interventions on levels of cycling and physical activity is necessary not only to inform future strategy and policy but also to strengthen the case that promoting cycling represents extremely good value for money for both individual and public health.

Ethnic density and mental health

The association is clear but the underlying mechanisms are not

In the linked study, Das-Munshi and colleagues investigated whether living in areas where higher proportions of people of the same ethnicity reside protects against common mental disorders.1 They also searched for mediating effects, particularly reduced exposure to racism and improved social support. They found a protective effect for some minority groups (particularly Irish and Bangladeshi people) but that support and discrimination were not key mediating factors. Indeed they suggest that ethnic density mechanisms are likely to be heterogeneous and may not operate the same way across groups.

The notion of an effect of ethnic density is not new. The idea that living in an area with a high own ethnic group density may be protective for mental health was first noted in the early 20th century. In 1928, Robert Park began the debate by writing about how migrants represent “marginal man,” breaking the “cake of custom.”2 A decade later,3 the interaction between individual ethnicity, neighbourhood ethnic composition, and the risk of admission to hospital for psychiatric illness in Chicago was reported. White people had lower admission rates than black people except when they lived in predominantly black areas, and in these areas black people had unexpectedly low rates of admission.

More recently an association between ethnic density and hospital admission rates for psychiatric illness in the United States was reported.4 In the United Kingdom, older national studies found no association between ethnic density and incidence of schizophrenia.5 However, several more recent locally based studies, many based on service contact data, have repeatedly suggested the presence of an ethnic density effect for a variety of mental health outcomes. For example, an ecological study found an inverse dose-response relation between the proportion of people from a non-white ethnic minority group living in an area of London and their incidence of schizophrenia.6

There has been much speculation about the underlying processes behind the ethnic density effect. Some have argued that minorities may experience more overt discrimination or institutionalised racism and be less able to access culturally specific facilities and services.7 A qualitative study based in London suggested perceived exclusion by some ethnic minority residents from local community networks, a need to rely on geographically dispersed culturally specific services and facilities, perceived risk of physical and psychological intimidation, and damaging effects of everyday racism.8 Das-Munshi and colleagues’ study adds to this literature through the use of nationally representative survey data, rather

9 De Hartog J, Boogaard H, Nijland H, Hoek G. Do the health benefits of cycling outweigh the risks? Environ Health Perspect 2010;118:1109-16.
than service contact data, and by highlighting the messy complexity of the association between ethnic density and mental health.

Das-Munshi and colleagues’ study uses data from the ethnic minorities psychiatric illness rates in the community survey (EMPORIC), which is a decade old. This reduces its relevance a little in that the ethnic profile of England has changed slightly. Data from the Office for National Statistics show that between 2001 and 2007, the white Irish and white British groups had an estimated annual growth rate of 1.6% and −0.1%, respectively, whereas the Indian and Asian Pakistani groups both grew at around 3.9% a year. The “white other” ethnic group, which makes up 3.5% of the population and grew at an annual rate of 4.8% between 2001 and 2007, is also not included. It would be interesting to know if, for example, Eastern European “marginal man” fares differently from other minority groups.

So where does this leave the debate? A growing body of evidence—which is fairly consistent across time, place, and ethnic group—now shows that ethnic density affects mental health. Das-Munshi and colleagues’ study leaves us more convinced of the effect, but further research is needed to clarify the scope and size of the effects, including the “tipping point” or degree of density needed to exert a protective effect on health. Above all, it highlights the need for further hypotheses about underlying mechanisms.


Changes in university funding for medical education in England
All students can afford quality education when they earn medical salaries

Opportunity costs money, and nobody likes paying. Amidst the alarm, considerable positivity greeted the report Securing a Sustainable Future for Higher Education. This is no mean achievement for the committee led by Lord Browne of Madingley. Principled and rationally argued, the report manages to avoid boxing politicians into corners on the sensitive issue of funding a competitive university industry, which is regarded as essential to future national prosperity. Few people would argue with the assertions that higher education is currently in crisis, and that current funding arrangements are not sustainable.

In the United Kingdom, students, their families, and the state all contribute to funding university education. This would continue under the Browne proposals, but the onus would change. With public finances under unprecedented pressure, the challenge is to match or exceed the investment of other countries in their university systems.

Browne cites global reports showing that the UK is at a competitive disadvantage because of its “inadequately trained workforce”—in 2010 it was ranked 55th out of 139 countries on the quality of its maths and science education. Medicine is recognised as being important to the wellbeing of our society and to our economy, and the committee acknowledges the risk that if the charges to students for clinical courses reflected the high costs, students would opt for courses that cost less. The report, permeated by implicit faith in the market economy and explicit commitment to student choice, proposes that public investment should continue to support priority courses—including medicine, nursing, and other healthcare degrees—with oversight from the new Higher Education Council.

Browne proposes no limit on fees charged by universities. Instead, government would pay the fees and reclaim the money from students when they can afford to pay. This is a straightforward fee of up to £6000 (€6825; $9600) a year. Above that figure universities would pay a tapered uncapped levy on all fees. Thus, whereas a university that charged students £6000 would keep all that income, one that charged £9000 would keep only £7650, with £1350 going to government to help cover the cost of providing students with upfront finance.

The committee strives to support the principle that “everyone who has the potential should be able to benefit from higher education.” Public concern has been that long courses like medicine could seem prohibitively expensive as fees rise and thereby skew applications towards students from richer families. UK medical courses already struggle more than other university courses to admit a proportionate number of students from lower socioeconomic backgrounds. Browne proposes that students will not have to pay any tuition fees up front and will begin to repay the cost of their fees only when their earnings reach £21 000. Medical graduates, who will probably exceed this threshold as soon as they qualify, will then begin to pay their loans back with low interest. All students would be entitled to flat rate maintenance loans of £3750 a year, which would replace the current means tested system. Additional grants (that do not need to be paid back) of £3250 a year are proposed.

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Patients seeking treatment abroad
Another challenge for general practice commissioning

If Andrew Lansley’s proposals for reorganisation of the NHS survive parliamentary scrutiny, large numbers of general practice commissioning groups will soon be taking responsibility for purchasing much of the specialist care provided to their patients.1 Many of these groups may already be thinking how they will deal with a very different set of providers, including increasingly independent foundation trusts, some of which may have become social enterprises outside the NHS, and an expanded private sector. They may have given less thought to those patients who choose to seek treatment abroad. Yet they may need to, and as a recent court ruling illustrates,2 this may be more complicated than they realise.

Although the number of patients seeking treatment elsewhere in the European Union is small,3 this could easily change, especially if people are faced with growing waiting lists or other forms of rationing as the new groups seek to control their budgets. British residents have had the right to obtain treatment in another EU country since 1971.4 Initially, the opportunities were limited mainly to people who fell ill when abroad or, less often, when the NHS agreed that there was too long a waiting list.5 Today, the use of such arrangements is increasing, especially if people are faced with growing waiting lists or other forms of rationing as the new groups seek to control their budgets. British residents have had the right to obtain treatment in another EU country since 1971.6 Initially, the opportunities were limited mainly to people who fell ill when abroad or, less often, when the NHS agreed that there was too long a waiting list.7 Today, the use of such arrangements is increasing, especially if people are faced with growing waiting lists or other forms of rationing as the new groups seek to control their budgets. British residents have had the right to obtain treatment in another EU country since 1971.8 Initially, the opportunities were limited mainly to people who fell ill when abroad or, less often, when the NHS agreed that there was too long a waiting list.9 Today, the use of such arrangements is increasing, especially if people are faced with growing waiting lists or other forms of rationing as the new groups seek to control their budgets. British residents have had the right to obtain treatment in another EU country since 1971.10 Initially, the opportunities were limited mainly to people who fell ill when abroad or, less often, when the NHS agreed that there was too long a waiting list.11 Today, the use of such arrangements is increasing, especially if people are faced with growing waiting lists or other forms of rationing as the new groups seek to control their budgets.

For those who accept that the interests of students wishing to study medicine have been fairly and squarely tackled in the Browne report, the important focus for medical education is to predict the impact on the university system and on medical schools in particular. Competitiveness is explicitly encouraged by the committee placing confidence in informed student choice to drive up quality. Media focus has been on the potential for universities to fail, yet, somewhat confusingly, the report supports a power for the Higher Education Council to bail out struggling institutions. Medical schools, unlike some schools for the other healthcare subjects, are generally part of the stronger universities, so closure of the parent organisation seems unlikely.

What remains to be seen is how the allocation of medical student numbers will play out in future. If student choice is the most powerful driver, then no medical school can rest on its laurels because presumably the Higher Education Council will ensure that essential funding support for clinical education is directed towards the courses on which students wish to enrol, and fierce intraregional competition between schools can be anticipated. Recognition and reward for teachers are the key to developing world class medical teaching that delivers value to students and patients.

The principles of the Browne report need to be accepted, along with their philosophy that sees higher education as a precious resource supporting the country’s future wellbeing. Much work needs to be done collaboratively between the Higher Education Council, NHS workforce planners, and those responsible for postgraduate medical education, including Medical Education England and the General Medical Council. The objective must be to equip the most able students to practise medicine in the best interests of UK patients. Properly nurtured students must be trained in the best possible research based institutions and be confident that they can repay reasonable fees over a reasonable timescale.

example, a citizen of another country resident here returning home to give birth).

To the dismay of several countries, including the United Kingdom, the situation changed dramatically in 1998. Two patients from Luxembourg argued that their health insurer could not restrict their right to be reimbursed for health services (in their cases dental treatment and spectacles) in another member state. The European Court of Justice agreed with them. A major consideration had been that these services were not provided in hospitals so, even if large numbers of people crossed borders to take up this right, it could not destabilise existing hospital provision.

These cases set an important precedent but, as with all groundbreaking cases, there was extensive debate about what they meant for healthcare in general. Would the ruling apply to national health services or only social insurance systems? What comprised hospital care? How would levels of reimbursement be set when countries had different prices? A series of further cases allowed these questions to be largely resolved. The crucial distinction was between hospital care (treatment that can be provided only within a hospital setting) and non-hospital care. In the first case, patients had to apply for authorisation to go abroad, but their healthcare funder could not deny them as long as the treatment was deemed medically necessary (taking account of international medical opinion and not just their own views); it would normally be provided in their home state; and it was not being provided in good time, taking account of their medical condition. In the case of non-hospital care, patients could go abroad freely without seeking authorisation.

Some national governments, especially those that had traditionally controlled costs in part by limiting supply, such as the UK, viewed this situation as highly unsatisfactory. Even the European Court of Justice recognised that it was undesirable to allow the steady accumulation of case law to establish policy. Yet, although all of the member states sought clarity, which could be achieved only by primary legislation, they could not agree what the new system of patient mobility would look like. Earlier this year, the Spanish presidency of the EU overcame this log jam to design a proposal that the member states could support, but this is now stuck in the European Parliament. As a consequence, the court has continued to step into the breach when required.

The most recent occasion was earlier this month, in a case where the European Commission had initiated proceedings against France for allegedly restricting patient movement. French insurers had demanded that anyone going abroad to use certain “major medical equipment,” such as cyclotrons, positron emission tomography scanners, and magnetic resonance imagers, had to seek prior authorisation in order to claim reimbursement. The European Commission argued that this was illegal because although these facilities were often located in hospitals, they need not be. The court upheld the French argument, on the basis that, like hospitals, it was necessary that European law did not threaten a system of planning that would ensure an appropriate geographical distribution of such costly equipment.

This ruling is important because it begins to clarify the previously uncertain legal interface between hospital and non-hospital care. It is not whether complex treatments must or must not be provided in a hospital setting. Rather, it is whether their cost and the importance of avoiding waste from the underuse of facilities demands that their distribution be subject to planning. It also supports the English Department of Health’s revised advice, issued earlier this year, which—although it reminded commissioners of the necessity of complying with European Court rulings—highlighted the lack of clarity about use of specialised or cost intensive equipment or infrastructure.

If general practice commissioning groups do come about they may not have to deal with many patients who choose to obtain treatment abroad, but they should be aware that some may exercise their rights to do so. Where this involves inpatient care or “major medical equipment” they will need to establish mechanisms for authorisation that must be based on criteria that are “objective, non-discriminatory, known in advance, in such a way as to circumscribe [their] discretion so that it is not used arbitrarily.” Quite how they will do this remains to be seen.

2 European Court of Justice. Case C-512/08 (European Commission v French Republic), 5 October 2010.
5 European Court of Justice. Case C-158/96 [Raymond Kohli v Union des Caisses de Maladie], 28 April 1998.
6 European Court of Justice. Case C-120/95 [Nicolas Decker v Caisse de Maladie des Employes Prives], 28 April 1998.
8 European Court of Justice. Case C-368/98 [Vanbrakel and others v Alliance nationale des mutualités chrétiennes (ANMC)], 12 July 2001.
9 European Court of Justice. Case C-372/04 [Yoanne Watts v Bedford Primary Care Trust], 16 May 2006.