converts arachidonic acid to prostaglandins. So the straightforward explanation of how these drugs might reduce the risk of Alzheimer's disease is that they attenuate pro-inflammatory prostanoid synthesis. There is, however, another possibility. In cell lines and mouse models of Alzheimer's disease, a subset of non-steroidal anti-inflammatory drugs including ibuprofen, indomethacin, and sulindac has been found to reduce production of the 42 residue β amyloid peptide independently of changes in cyclo-oxygenase activity.[7] Instead the effect seemed to be mediated through changes in the proteolytic processing of the amyloid precursor protein.

One reason then for the discrepancy between the conclusions of the systematic review of observational studies and the results of the randomised controlled trial might be that the trialists chose the wrong anti-inflammatory drugs. Another is that although these drugs are ineffective in established disease, they do exert a beneficial effect in the presymptomatic stage of the illness. A trial in progress may resolve both of these points: ibuprofen and the selective cyclo-oxygenase-2 inhibitor celecoxib are being compared with placebo in a group of people who, because of their family history, are at high risk of Alzheimer's disease.[8]

We also have to face the possibility that, despite the best efforts of the investigators, the results of the observational studies that reported a protective effect were distorted by some unmeasured confounding variable. After all, it is not hard to imagine that the sort of people who need to take non-steroidal anti-inflammatory drugs in the long term have a way of life or a genetic constitution that reduces their susceptibility to Alzheimer's disease—even if it is impossible to say precisely what the protective factor might be. If this view seems unnecessarily bleak, remember the story of hormone replacement therapy. Here too, the observational studies indicated that it protected against cognitive decline. Plausible mechanistic explanations were invoked.[9] But the results of a large randomised controlled trial, the women's health initiative memory study, showed that women taking a combination of oestrogen and progestogen actually experienced higher rates of dementia and cognitive decline than those taking placebo.[10 11]

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Treatment of anal fissure

Medical treatments are only marginally better than placebo, but surgery may cause incontinence

Anal fissure is one of the most common lesions to consider in the differential diagnosis of anal pain. This is an ulcer in the squamous epithelium of the anus located just distal to the mucocutaneous junction and usually in the posterior midline. It typically causes episodic pain that occurs during defecation and for one to two hours afterwards.[1] This feature uniquely distinguishes anal fissure from other causes of anal pain such as thrombosed haemorrhoids, abscess, viral ulcers, and others. Atypical fissures may be multiple or off the midline, or be large and irregular. These may be caused by inflammatory bowel disease, local or systemic malignancy, venereal infection, trauma, tuberculosis, or chemotherapy. The cause of the typical or benign fissure is not clear nor are there accepted methods for the prevention of fissures—both fertile areas for research.

The most consistent finding in typical fissures is spasm of the internal anal sphincter, which is so severe that the pain caused by the fissure is thought to be due to ischaemia of the sphincter.[2] Relief of the spasm has been associated with relief of pain and healing of the fissure without recurrence. Historically the most common approach for relieving the pain associated with spasm of chronic adult anal fissure is surgical, though no placebo controlled surgical trials have been undertaken. Morbidity from operative procedures, mainly incontinence, was once thought to be extremely rare[3] but has been substantial in some recent reports.[4] So by the late 1990s when alternatives to surgery were sought because of cost, time for recovery, and risk of incontinence, rather than turn back to older treatments, such as lubricants and numbing agents, newer medications were investigated—in each case a medication that was known to relax muscle spasm. These have included nitroglycerin ointment, injection of botulinum toxin, and calcium channel blockers either given as tablets or applied topically.

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The choice of treatment remains difficult for the following reasons. Although surgery is highly efficacious and succeeds in curing the fissure in more than 90% of patients, in a systematic review of randomised surgical trials the overall risk of incontinence was about 10%.[5] This was mostly incontinence to flatus, and there are no reports delineating the duration of this problem (is it permanent or transitory?) Publications describing treatment for incontinence after sphincterotomy for fissure are strikingly absent, implying a lack of need compared with other incontinent populations.

Regarding medical treatment, in a similar systematic review combining all analyses in which a placebo was used as the comparison group,[6] the healing rate in the placebo group was found to be 35%. This was a level of response that was fairly uniform across studies (standard deviation 12%). The medications being tested in the meta-analysis (nitroglycerin ointment, botulinum toxin injection, and calcium channel blockers) must have their efficacy viewed in the context of this placebo effect and also in the context of a cure rate for surgery that often exceeds 95%.[5] In the combined analyses, nitroglycerin ointment was found to have a healing rate of about 55%. In comparisons of nitroglycerin ointment to botulinum toxin injection or calcium channel blockers, no significant difference in efficacy was found between the three. Overall nitroglycerin ointment was more effective than placebo, but in sensitivity analyses that excluded studies with placebo cure rates below 10%—more than two standard deviations below the mean—statistical evidence of efficacy disappeared. In addition, with nitroglycerin ointment, the most investigated medical treatment, headache was common, occurring in almost 40% of subjects in the combined analyses and severe enough often to stop treatment.[6]

So it would be advantageous if the risk of incontinence could be reduced after surgery or the success rate of medical treatments increased to that found in surgery, but with less risk of headache. The Cochrane reviews provide some direction here but not a quick fix. Anal stretch was found to have a significantly higher risk of incontinence than controlled sphincterotomy in surgical trials and a higher risk of treatment failure. Stretch should probably be abandoned in favour of partial internal sphincterotomy until a better operation is described. Among the medical treatments, calcium channel blockers applied topically caused fewer headaches and may be as efficacious as nitroglycerin ointment.

Medical treatment for chronic anal fissure, acute fissure, and fissure in children may therefore be applied with a chance of cure that is only marginally better than placebo. The risk of using such treatments is not great: mainly headache during the use of nitroglycerin ointment, without apparent adverse effect in the long term. Medical treatments can therefore be used in individuals wanting to avoid surgical treatment, and surgery can be reserved for treatment failures in adults with chronic typical fissure. Topical application of calcium channel blockers may be as effective as nitroglycerin ointment in the treatment of anal fissure, without the risk of headache, which many patients find unacceptably painful. Too few studies exist to establish this efficacy.

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Treatment of postmenopausal osteoporosis

Choice of treatment depends on efficacy, individual risk profile, and side effects

Osteoporotic fractures in older women constitute a major cause of disability, mortality, and economic burden.[1] The incidence of fractures related to osteoporosis will increase worldwide over the next three decades as the proportion of women over the age of 65 increases.[2] It is therefore important that we identify efficacious treatments that will reduce the incidence of osteoporotic fractures. In the past, randomised controlled trials have focused on the surrogate outcome of bone mineral density. The limitation of relying on a surrogate outcome was highlighted by the results of earlier trials, in which increases in bone density did not translate into decreased risk of fracture.[3] As a result of stricter standards that required evidence of efficacy against fractures for drug approval, we now have large randomised trials with prevention of fractures as an outcome. Data from these trials provide information on the strength of the evidence for efficacy of the different treatments.

Evidence based reviews of treatments for postmenopausal osteoporosis have confirmed which treatments reduce the risk of fractures in women with osteoporosis.[4–6] Most currently used drugs are antiresorptive agents that reduce osteoclast mediated resorption and bone remodelling. Potent bisphosphonates include alendronate and risedronate, which reduce the relative risk of vertebral fractures by 40-50%. Both of these bisphosphonates also reduce the relative risk of non-vertebral fractures (for example, fractures of the hip and wrist) by 40-50% and are now considered to be first line agents for the prevention and treatment of postmenopausal osteoporosis.

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