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integrated specialist teams can deliver high quality care to these vulnerable patients.

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Contributors: All authors helped to formulate the study design, coordinate the collection of data, and write the paper. CB undertook the data evaluation and will act as guarantor.

Funding: None.

Competing interests: None declared.

1 Kitwood T, Bredin K. *Evaluating dementia care: the DCM method.* 7th ed. Bradford: Bradford Dementia Research Group, 1997.

2 Brooker D. Looking at them looking at me. A review of observational studies into the quality of institutional care for elderly people with dementia. *J Ment Health* 1995;4:145-56.

3 Copeland JR, Kelleher MJ, Kellett JM, Gourlay AJ, Gurland BJ, Fleiss JL, et al. A semi structured clinical interview for the assessment of diagnosis and mental state in the elderly. The geriatric mental state schedule: development. *Psychol Med* 1976;6:439-49.

4 Leaper R, ed. *Training and qualifications for work with older people. Report of a national conference with recommendations for action. National Council on Ageing.* London: Age Concern, 1998.

5 Department of Health. *Fit for the Future? National required standards for residential and nursing homes for older people.* London: DoH, 1999. www.doh.gov.uk/pub/docs/doh/fitfuture.pdf (accessed 9 May 2001).

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Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study

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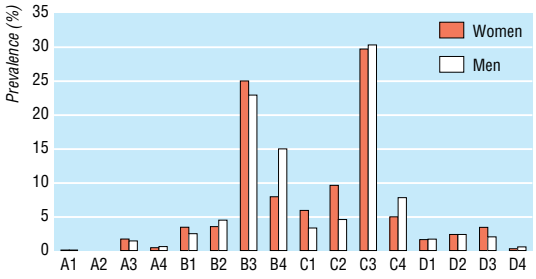
The growing use of pharmacological agents means that drug interactions are of increasing interest for public health.[1] Monitoring of potential drug interactions may improve the quality of drug prescribing and dispensing, and it might form a basis for education focused on appropriate prescribing.

Participants, methods, and results

In a cross sectional study, we analysed all prescriptions (n=962 013) involving two or more drugs dispensed to the Swedish population (n=7 214 509; age range 15-95) from all Swedish pharmacies (n=885) in January 1999. The data were taken from the Swedish healthcare database on pharmaceutical agents, which records all prescriptions dispensed at all of the pharmacies in Sweden. Strict registration routines and internal controls support the accuracy of the database.

Data were stratified by age and sex, and odds ratios were calculated using multilevel logistic regression.[2] Potential drug interactions were classified according to clinical relevance (types A, B, C, and D) and documented evidence (types 1, 2, 3, and 4)—for example, subtype D4 indicates an interaction with greater potential clinical relevance than that classified as subtype A1 (figure).[3 4]

Of the 962 013 prescriptions dispensed by pharmacies, 130 765 (13.6%) included at least one potential drug interaction. The number of potential drug interactions increased with the patient's age and with the number of drugs per prescription (data not shown). Clinically relevant potential drug interactions that could be controlled by adjusting the dose (type C) were found in 29 991/371 402 (8.1%) men and 44 754/545 857 (7.6%) women. Potential interactions that might have serious clinical consequences (type D) were found in 13 282 (1.4%) of the prescriptions (11.4% (5269/371 402) men and 1.4% (8013/590 611) women). However, 6936 (52.2%) of these potential interactions were between ipratropium and β adrenergic agonists, which result in an increased risk of acute angle closure glaucoma only when the drugs are used in nebulised form—an uncommon treatment.



Clinical relevance:
A = Probably no clinical relevance.
B = Clinical relevance not completely assessed.
C = Clinical relevance. Interaction may modify the effect of the drug, but this is susceptible to control by dose adjustment (includes both beneficial and adverse drug interactions).
D = Clinically relevant. Interaction may have serious clinical consequences, may suppress a drug effect, or the effect modification is difficult to control by dose adjustment. This type of drug interaction ought to be avoided.

Documented evidence:
1 = Incomplete case reports, in vitro studies, or a drug interaction is presumed on the basis of evidence coming from similar drugs.
2 = Well documented case reports.
3 = Based on studies in volunteers or on pilot studies in patients.
4 = Based on controlled studies in relevant patient groups.

Prevalence of potential drug-drug interaction subtypes[3 4] among 962 013 prescriptions containing two or more drugs dispensed to patients aged 15-95 from Swedish pharmacies in January 1999.

After adjusting for the number of drugs dispensed, we found that combinations of drugs with potential interactions that may have serious clinical consequences (type D) were less likely to be prescribed to women than men (relative risk 0.88; 95% confidence interval 0.85 to 0.92).

Of the potential type D interactions, 2358 were between potassium supplements and potassium sparing diuretics—a combination that may result in severe and even life threatening hyperkalaemia. The combination of warfarin dispensed with a non-steroidal anti-inflammatory drug (subtype D4), which can increase the risk of gastrointestinal bleeding due to gastric mucosal damage by the non-steroidal anti-inflammatory drug and the anticoagulant effect of warfarin, was found on 644 occasions.

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Dextropropoxyphene was dispensed with alprazolam on 261 occasions (this combination may increase the central depressant effects of alprazolam) and with carbamazepine on 240 (this combination may cause serious toxic effects by increasing plasma concentrations of carbamazepine). Cisapride was dispensed with erythromycin on five occasions, with clarithromycin on three, fluconazole on 24, and itraconazole on one; any of these combinations may result in torsades de pointes, syncope, cardiac arrest, and sudden death.

Comment

Although the percentage of potential drug interactions that may have serious clinical consequences (type D) was low (1.4%), serious and potentially fatal drug interactions—for example, NSAID and warfarin, potassium supplements and potassium sparing diuretics, dextropropoxyphene and carbamazepine, and cisapride and fluconazole—were detected. The risk of interactions with cisapride was known in 1996,[5] and cisapride, which is still available in Sweden, is being withdrawn in many countries.

Prescribing pairs of drugs with potential interactions increases the risk of, but need not lead to, an adverse reaction. Many drug interactions are susceptible to control by dose adjustment; moreover, some are beneficial and are exploited in therapeutics.

National monitoring of potential drug interactions in Sweden is feasible. Differences in healthcare systems need to be considered when extrapolating the results of this study to other countries.

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Contributors: JM had the original idea for the article, designed and performed the analysis and interpretation of the data, and drafted, wrote, and revised the content. JF programmed the database. All authors were involved in the study design, data interpretation, content revision, and approval of the final version. JM is the guarantor of the paper.

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Competing interests: None declared.

1 Stockley IH. *Drug interactions: a source book of adverse interactions, their mechanisms, clinical importance and management.* London: Pharmaceutical Press, 1996.
2 Rasbash J, Browne W, Goldstein H, Yang M, Plewis I, Healy M, et al. *A user's guide to MLwiN.* London: Institute of Education, University of London, 1999.
3 Sjöqvist F. Drug interactions. In: *The Swedish Drug Compendium "FASS". Läkemedel i Sverige. Förtecking över humanläkemedel.* Stockholm: LINFO Läkemedelsinformation AB, 1999:1383-1453.
4 Sjöqvist F. Drug interactions. In: *The Swedish Drug Compendium "FASS". Läkemedel i Sverige. Förtecking över humanläkemedel.* Stockholm: LINFO Läkemedelsinformation AB, 2000:1481-1556.
5 Biverkningsinformation: Prepulsid (cisaprid) - hjärtarytmi: Påminnelse. Information från Läkemedelsverket 1996;7(6):27.

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Rationing in the NHS: audit of outcome and acceptance of restriction criteria for minor operations

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General practitioners' referrals for skin lesion excisions constitute a large proportion of cases seen at plastic surgery clinics. Escalating rates of skin cancer have increased the numbers of urgent referrals due to suspicious looking skin lesions. As a result, patients with clinically benign lesions spend long periods on waiting lists, exceeding the waiting times agreed in negotiated contracts.

In March 1999, a total of 666 patients had been waiting over one year for minor plastic surgery at Salisbury District Hospital. In response, Salisbury Health Care NHS Trust and Wiltshire Health Authority proposed a new system of contract exclusions, whereby only patients with lesions that suggested malignancy or that were disfiguring or potentially disfiguring would be seen. The health authority and the trust assumed that excluded patients would not be seen or treated elsewhere. The consultant plastic surgeons reviewed the referral letters for patients who were not given an operation and returned the letters with explanatory notes.

This study aimed to assess the acceptability of the new system among patients and general practitioners and to determine the outcome of cases excluded under the new criteria.

Methods and results

Details of all referrals rejected under the new system were collected for six months after its inception on 1 September 1999. In each case, the site and description of the lesion were recorded. General practitioners and patients were contacted by telephone to assess their satisfaction with the system and to determine whether further referrals for excision had been made. The histological diagnosis was obtained for lesions excised after re-referral.

In six months, 112 referrals were rejected. Of these, 99 contactable patients (134 lesions) were followed up; 103 lesions (77%) were in the head and neck. In many referral letters the clinical description was non-specific but did not suggest malignancy or disfigurement.

Nineteen (19%) patients later had their lesions excised; 18 patients had benign pathology, and one had a squamous cell carcinoma. The patient with the carcinoma had been refused treatment solely on the basis of a referral letter—on grounds that this was a cosmetic problem—and afterwards sought a private consultation and subsequent excision.

For those technologies for which cost per QALY or per life year was cited, all received positive recommendations, and all but one (riluzole) had cost per QALY below £30 000. The imposition of restrictions on recommended use generally reduced the cost per QALY. Patients' values were cited as the reason for recommending riluzole for motor neurone disease (amyotrophic lateral sclerosis form only), despite its relatively high cost per QALY of £34 000-44 000. NICE cited "the severity and relatively short life span of people with ALS and in particular … the values which patients place on the extension of tracheotomy free survival time."[10]

The provisional guidance that recommended against the use of beta interferons and glatiramer for multiple sclerosis cited their relatively high cost per QALY (£40 000 to £90 000 on the most optimistic estimates) and stated that NICE had in mind the cost effectiveness ratio of technologies it had previously recommended.[11]

The final element of each NICE guidance concerns the costs to the NHS of implementing the guidance (cost impact). Estimates of gross and net costs are provided, the latter taking into account any substitution of old technologies by new ones. The items that led to major increases in net costs were tribavirin and interferon alfa, both prescribed for hepatitis C (£55m in total, possibly spread over several years, and due mainly to a backlog of untreated cases) and glycoprotein IIb/IIIa inhibitors for acute coronary syndromes (net £30m-31m), with none of the others costing more than £20m. The impact on total net cost was reduced by projected savings for some technologies—notably, restricted use of proton pump inhibitors (projected saving £40m-50m annually). The combined net cost of the 22 judgments was £200m-214m or around 0.5% of annual NHS spending in England and Wales. This provides some indication, on the basis of individual technologies, of the extent to which new health technologies may change net healthcare spending. Increases of this magnitude should be readily achieved within the real increases in NHS spending of around 6% per year over the three years to 2004, although some local bottlenecks may become apparent.

Discussion

While NICE has been caricatured under the heading "it's easier to say yes than no,"[12] it would be more accurate to characterise it as saying "yes, but …" Its recommendations have all cited evidence of clinical benefits, while only around half have cited cost per QALY. Many of its recommendations have specified conditions for use, such as subgroups of patients most likely to benefit. This in turn requires guidelines covering the full range of treatment options for the different groups of patients. This second, guideline, function of NICE may prove more important and challenging over the longer term, given the magnitude of the task and the paucity of evidence. By October 2000 NICE had published four guidelines and was working on a further 31, often for the same diseases as those for which guidance on technologies has been issued.

The specification by NICE of conditions for use, which has generally enabled it to keep the cost per QALY below £30 000, could be seen as requiring rationing at a more detailed level, perhaps within some overall guidelines for use. Overall, however, NICE's guidance recommending use of most technologies appraised will arguably lead to "faster and more uniform access" to these technologies rather than to denial access.

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Competing interests: The author directs a unit that contributes health economics input to NICE assessments. He is also a codirector of the National Horizon Scanning Centre. The views expressed in this article are personal and do not reflect those of any organistion.

1 Department of Health. *The new NHS: dependable, modern*. London: Department of Health, 1997.
2 Sculpher, M, Drummond M, OBrien B. Effectiveness, efficiency, and NICE [editorial]. *BMJ* 2001;322:943.
3 Newdick C. Strong words. *Health Service J* 2001;111:26-7.
4 NICE. *NICE technology appraisal programme. Arrangements for receiving comments on appraisal consultation documents. Item 5: Technology appraisal programme. Consultation on the proposed publication of provisional and final determinations.* Minutes of NICE board meeting, 6 February 2001. www.nice.org.uk/pdf/brdfeb01item5.pdf (accessed 1 Oct 2001).
5 Department of Health. *Faster access to modern treatment; how NICE appraisal will work*. Leeds: NHS Executive, 1999.
6 NICE. *NICE technical guidance for manufacturers and sponsors on making a submission to a technology appraisal*. London: NICE, 2001.
7 House of Commons Health Committee. *Health—minutes of evidence. 8 November 2000*. www.parliament.the-stationery-office.co.uk/pa/cm199900/cmselect/cmhealth/cmhealth.htm (accessed 1 Oct 2001).
8 NICE. *Guidance for appellants. Technology appraisal process, 2*. www.nice.org.uk/pdf/guidanceforappellantsfinal.pdf (accessed 1 Oct 2001).
9 Department of Health and Association of British Pharmaceutical Industry. Prime minister announces results of pharmaceutical industry competitiveness task force. Press release. 28 March 2001. www.abpi.org.uk (accessed 1 Oct 2001).
10 NICE. *Riluzole for motor neurone disease—full guidance*. London: NICE, 2001. wwe.nice.org.uk/Article.asp?a=14490 (accessed 27 March 2001).
11 NICE. *Beta interferon and glatiramer acetate in the treatment of multiple sclerosis. Provisional appraisal determination*. August 2001. www.nice.org.uk/Docref.asp?d=18759 (accessed 1 Oct 2001).
12 Smith R. The failings of NICE. *BMJ* 2000;321:1363-4.

Corrections and clarifications

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In this paper by Juan Merlo and colleagues (25 August, pp 427-8) we mistakenly omitted from the figure legend the number of possible drug interaction pairs. The legend should have read: "Prevalence of potential drug interaction subtypes[3 4] among the 191 899 possible drug interaction pairs found in the 962 013 prescriptions containing two or more drugs dispensed to patients aged 15-95 from Swedish pharmacies in January 1999."

Revisiting the Cochrane Collaboration

Geographical gremlins muddled the authors' addresses at the end of this article by Mike Clarke and Peter Langhorne (13 October, p 821). Dr Clarke is associate director at the Cochrane Centre, Oxford OX2 7LG, and Professor Langhorne is professor in the academic section of geriatric medicine at the Royal Infirmary, Glasgow G4 0SF.

Prospective health impact assessment: pitfalls, problems, and possible ways forward

We have electronic gremlins too at the *BMJ*. This time they pushed off a note that should have appeared in the margin of this article by Jayne Parry and Andrew Stevens (17 November, pp 1177-82). The note would have alerted readers to the fact that additional references appear on bmj.com (these are cited in the main text as w1 to w17).