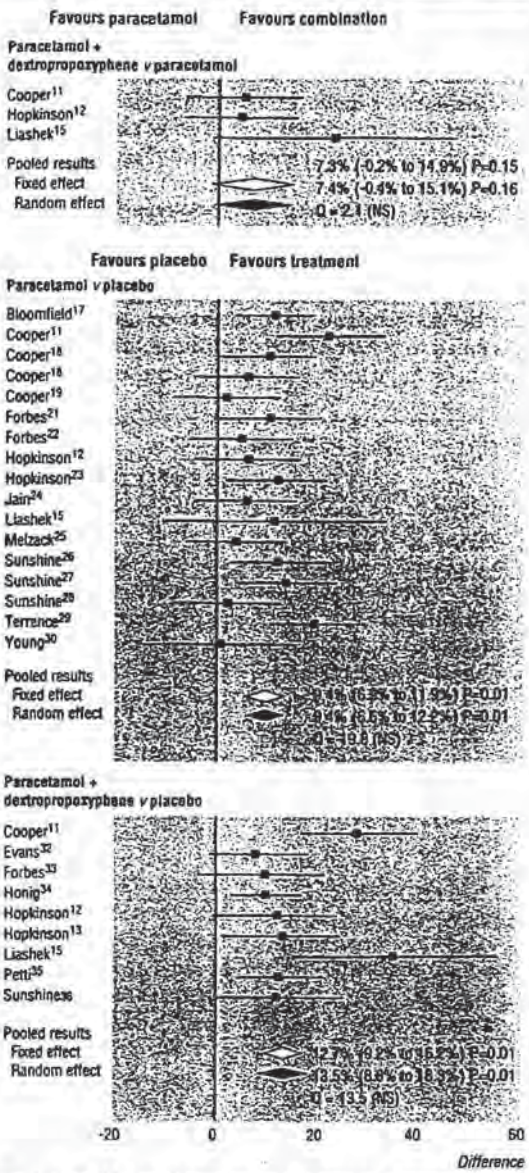

Fig 1 Mean (95% confidence interval) differences in percentage sum of differences in pain intensity between treatments

measured, necessitating variance imputation or sample size weighting when we pooled the data (see table 1).

Head to head comparisons

A total of 461 patients took part in six head to head, three armed trials with both active and placebo controls.[11-16] Two of these gave no data on the efficacy outcome measures in a form usable in our analysis.[14 16] Huskisson used pain relief scores and undertook multiple testing at six hourly time points over 6 hours and reported that at three of those time points co-proxamol was better than paracetamol 1000 mg but not at the other three.[14] No variance estimates were given. Messick on the other hand only reported mean pain score per hour, again without variance estimates.[16] The mean value reported (1.78 pain score units per hour for the combination, 1.89 for paracetamol 650 mg, and 1.81 for propoxyphene) suggested no sharp differences. The reported mean pain relief scores in per cent per day were 40.9, 39.5, and 39.0, respectively, again suggesting no obvious differences in efficacy. These two trials were the only two crossover trials retrieved by us. The results from the parallel group trials included in our meta-analysis indicate that both formulations were more effective than placebo, but there was no statistical difference in their efficacies on the basis of either the percentage sum of the pain intensity difference (see fig 1) or response rate ratio (see fig 2).

Indirect comparisons

A total of 397 patients participated in the paracetamol-dextropropoxyphene versus placebo trials. Figure 1 shows that the combination was effective, as shown by a pooled difference in sum of pain intensity difference of 12.7% (95% confidence interval 9.2 to 16.2%). Use of a random effects model led to the same conclusion (mean effect of 13.5%; 8.8% to 18.2%).

Overall, 1144 patients were included in the paracetamol versus placebo trials. These included patients from both the two-armed and three-armed studies. The pooled mean difference in the percentage sum of pain intensity difference was 9.4% (6.9% to 11.9%) with a fixed effects model and 9.4% (6.6% to 12.2%) with a random effects model, again indicating that paracetamol is an effective analgesic on the basis of this outcome measure.

Comparison of the effects estimated from the paracetamol-dextropropoxyphene versus placebo and the paracetamol versus placebo percentage sum of pain intensity difference (indirect estimation) failed to show any significant difference, as shown by the overlap of two sets of pooled confidence intervals (fig 1).

Use of the rate ratio of patients responding with moderate to excellent pain relief as a measure of efficacy yielded results consistent with the data on percentage sum of pain intensity difference. Both paracetamol and the paracetamol-dextropropoxyphene combination were more effective than placebo. There was no significant difference between the two paracetamol formulations, however, as shown by the overlap of two sets of pooled confidence intervals (fig 2). The random effects estimates should be used because of the heterogeneity of effects in the paracetamol versus placebo trials. Rate differences were 0.27 (0.17 to 0.38) for paracetamol and 0.24 (0.16 to 0.32) for paracetamol-dextropropoxyphene. A mean number needed to treat of 4 was obtained for both formulations by taking the inverse of rate difference in both cases. Compared with placebo, four subjects will on average require to be treated with either paracetamol or the combination for one more patient to obtain moderate to excellent pain relief.

Adverse effects

Comparison of side effect profiles showed that the combination of paracetamol and dextropropoxyphene caused more dizziness than placebo. On average, treating 42 patients will lead to one more patient complaining of dizziness than if they were receiving placebo. Surprisingly, paracetamol caused more drowsiness than placebo, an observation which clearly needs further confirmation because of its poor face validity. There was no difference in any of the reported side

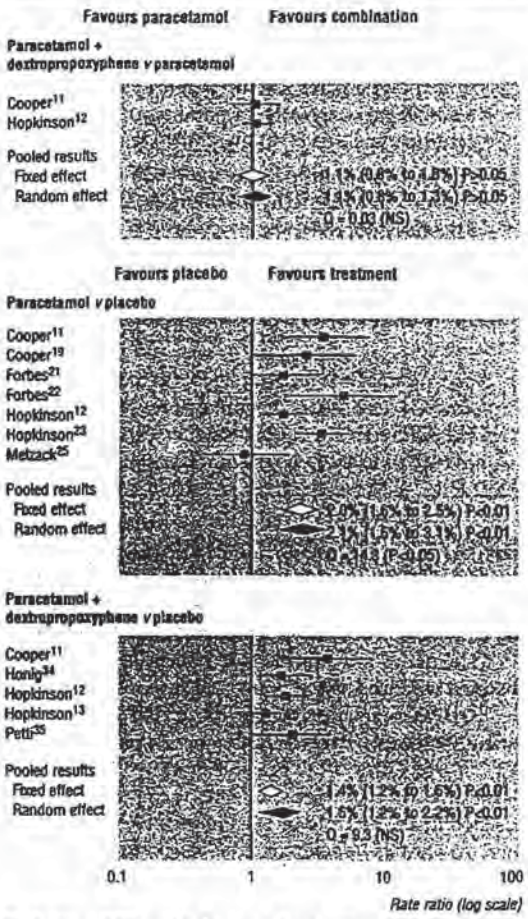

Fig 2 Mean (95% confidence interval) rate ratios for moderate to excellent pain relief between treatments

effects between paracetamol and its combination with dextropropoxyphene (table 3).

Sensitivity analysis for indirect comparison

Direct versus indirect comparisons—Two estimates of paracetamol-placebo effect were derived, one on the basis of the results of the head to head trials including a placebo arm and the other based on placebo controlled trials not including a paracetamol-dextropropoxyphene arm. This sensitivity analysis showed no difference in estimates of effect for placebo controlled trials in the two-armed studies (8.8%; 6.1% to 11.5%) when compared with the three-armed studies (14.1%; 6.9% to 21.4%). Similarly, for the combination product the estimated effect relative to placebo was no different in the two-armed studies (10.1%; 6.0% to 14.3%) than in the three-armed studies (19.3%; 12.8% to 25.9%). Both sets of trials therefore gave qualitatively consistent estimates (table 4), although the data suggest a more pronounced effect in the latter.

Method of analysis—Given that many of the studies considered in our meta-analysis failed to report on the variances associated with the estimates of effect, we undertook sensitivity analyses with respect to method of pooling. Firstly, we included only studies with variance estimates. Secondly, we used sample size weighting adopted by Eisenberg et al in their meta-analysis of non-steroidal anti-inflammatory drugs in cancer pain.[5] Thirdly, we used imputation of variance, whereby we assigned the pooled estimate of variance, calculated from studies reporting such values, to estimate variance for the 19 studies that had not done so (tables 1 and 2). Pooling only studies reporting variance showed that in the indirect comparisons the estimated effect size for paracetamol relative to placebo was 8.3% (2.7% to 13.9%) while for the combination analgesic the corresponding value was 9.4% (6.9% to 12.5%). These results show no difference in effect between paracetamol and the paracetamol-dextropropoxyphene combination. The head to head studies were not numerous enough for this sensitivity analysis. Use of sample size as weight provided pooled estimates of effect which were consistent with those seen when variance in studies not reporting them were imputed by using the pooled estimate of variance from studies that had, as shown in table 5. Irrespective of the method for imputing variance, paracetamol and paracetamol-dextropropoxyphene were both more effective than placebo, but there was no difference in their effectiveness.

Discussion

Our meta-analysis supports the claim of Sykes et al that paracetamol-dextropropoxyphene is effective as an analgesic.[2] Implicit in their response to Haigh's

Table 3 Comparison of risk of side effects (95% confidence intervals) with paracetamol, paracetamol plus dextropropoxyphene, and placebo

Comparisons	Any side effect	Nausea	Dizziness	Drowsiness	Headache
Paracetamol plus dextropropoxyphene v paracetamol					
Crude rate	16/117 v 25/112	10/234 v 8/229	7/234 v 6/229	10/229 v 12/229	1/234 v 5 / 229
Weighted relative risk	0.62 (0.35 to 1.10)	1.16 (0.47 to 2.85)	1.11 (0.37 to 3.36)	1.04 (0.40 to 2.69)	0.30 (0.05 to 1.93)
Weighted risk difference	−0.08 (−0.18 to 0.02)	0.007 (−0.03 to 0.04)	0.01 (−0.02 to 0.04)	−0.06 (−0.24 to 0.12)	−0.01 (−0.03 to 0.004)
Paracetamol v placebo					
Crude rate	64/345 v 48/355	16/355 v 14/362	11/364 v 9/372	43/ 378 v 24/389	13/427 v 17/431
Weighted relative risk	1.42 (1.01 to 2.02)*	1.14 (0.54 to 2.40)	1.24 (0.47 to 3.26)	1.77 (1.10 to 2.86*	0.79 (0.38 to 1.67)
Weighted risk difference	0.02 (−0.03 to 0.06)	0.003 (−0.03 to 0.03)	0.002 (−0.02 to 0.02)	0.02 (−0.01 to 0.05)	−0.01 (−0.03 to 0.01)
Paracetamol plus dextropropoxyphene v placebo					
Crude rate	24/167 v 28/239	13/295 v 10/367	14/316 v 5/388	15/279 v 10/356	7/295 v 18/367
Weighted relative risk	1.16 (0.69 to 1.97)	1.65 (0.73 to 3.69)	3.09 (1.07 to 8.87)*	1.69 (0.76 to 3.74)	0.70 (0.29 to 1.68)
Weighted risk difference	0.02 (−0.05 to 0.09)	0.02 (−0.01 to 0.05)	0.02 (0.0001 to 0.046)*†	0.02 (−0.01 to 0.05)	−0.03 (−0.06 to −0.01)*‡

*P≤0.05.
†Number needed to treat was 43 (21 to 6940).
‡Number needed to treat was −30 (−138 to −17) (favours paracetamol plus dextropropoxyphene—that is, fewer headaches in the active treatment group).

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Table 4 Sensitivity analysis (95% confidence interval)with respect to type of placebo controlled trials

Type of trial	Difference in SPID%	Response rate ratio*
Paracetamol *v* placebo		
Placebo trials in two armed studies	8.8 (6.1 to 11.5)	2.2 (1.6 to 3.0)
Placebo trials in three armed studies	14.1 (6.9 to 21.4)	1.9 (1.3 to 2.6)
Overall	9.4 (6.9 to 11.9)	2.1 (1.5 to 3.1)
Paracetamol plus dextropropoxyphene *v* placebo		
Placebo trials in two armed studies	10.1 (96.0 to 14.3)	1.7 (1.2 to 2.5)
Placebo trials in three armed studies	19.3 (12.8 to 25.9)	1.7 (1.1 to 2.6)
Overall	12.7 (9.2 to 16.2)	1.4 (1.2 to 1.7)

SPID=sum of pain intensity difference.
*Response rate ratio for patients receiving treatment relative to placebo. Response rate is defined as proportion of patients reporting moderate to excellent or more than 50% pain relief during observation.

Table 5 Sensitivity analysis with respect to method of variance imputation for difference in SPID% (95% confidence interval)

Detail	Pooled estimate weighted for sample size*	Pooled estimate weighted for variance†
Paracetamol *v* placebo (n=17)	7.9 (4.2 to 11.7)	9.4 (6.9 to 11.9)
Paracetamol plus dextropropoxyphene *v* placebo (n=9)	11.4 (6.8 to 16.0)	12.7 (9.2 to 16.2)
Paracetamol plus dextropropoxyphene *v* paracetamol (n=3)	5.3 (−2.7 to 13.2)	7.3 (−0.2 to 14.9)

SPID=sum of pain intensity differences.
*Mean difference in SPID% weighted for sample size as described by Eisenberg et al.[5]
†Mean difference in SPID% weighted for variance, with variance in studies not reporting them imputed by using pooled estimate from studies reporting variance.

criticism of the widespread use of paracetamol-dextropropoxyphene[1] was the assumption that the combination was more effective than paracetamol alone. Our systematic overview shows that the current data do not support this view. Happily, though, the incidence of adverse effects is no higher with the combination than with paracetamol alone. Single dose randomised controlled trials cannot be expected to capture estimates of potential for abuse, however, and this is a subject of concern with combination products containing centrally acting analgesics.[45]

In undertaking our meta-analysis, we were hampered by the absence of variance estimates in many of the trials. This is a problem which should decrease with the wider adoption of the CONSORT statement on the quality of reporting of clinical trials.[44] The fact that irrespective of the method of variance imputation the same qualitative results were obtained gives us some confidence with respect to the robustness of our conclusion; on current evidence, the combination of dextropropoxyphene 65/100 mg with paracetamol 650 mg is no better than paracetamol 650 mg on its own for the type of pain considered in this meta-analysis.

There were relatively few studies, and it is possible that we could have missed small additive analgesic effects of dextropropoxyphene. Our 95% confidence interval estimates suggest that the magnitude of effect observed is neither statistically nor clinically meaningful. The differences in effect between the combination and paracetamol in the head to head studies were 7.3% (−0.2% to 14.9%) on the basis of the percentage sum of differences in pain intensity and 1.1 (0.8 to 1.3) on the basis of response rate ratio. In an earlier communication we provided data to suggest that an analgesic effect of 7 (3 to 10) assessed by using percentage sum of differences in pain intensity, was not translated into an increased number of patients who obtained at least moderate pain relief.[1] While that study assessed the possible additive effect of different drugs (codeine and caffeine rather than dextropropoxyphene), the fact that all three drugs are centrally active and that the same measure (percentage sum of pain intensity difference) was used suggests that comparison of the two sets of results is reasonable.

To explain why discordant conclusions may be obtained when relative efficacy and response rate ratio are used as outcomes, we propose that although a patient may well perceive a difference in pain intensity, this change may not be sufficient to be judged important. In other words, a decrease in pain intensity, reflected in the percentage sum of pain intensity difference, may not be sufficient for the patient to classify this change as a categorical change—for example, from severe to mild and reflected in response rate ratio as an outcome measure.

It has been suggested that as dextropropoxyphene is subject to a high first pass metabolism[45] single dose studies are inadequate to estimate the efficacy of the drug. In the only two multiple dose studies we could identify a beneficial effect over and above that of paracetamol was not detected.[10,31] We concur with the view of Miller et al that the popularity of the paracetamol combination does not lie in improved efficacy.[46]

Key messages

- Combinations of paracetamol with centrally acting analgesics are widely used, accounting for 73% of all prescriptions for paracetamol in a recent hospital survey in the United Kingdom
- The combination of paracetamol (650 mg) with dextropropoxyphene hydrochloride (32.5 mg) is particularly popular
- In both head to head and indirect comparisons of paracetamol and the combination, the combination was no better than paracetamol on its own
- Since the total number of patients in the few published head to head comparisons was modest, small differences in effect cannot be excluded but these are unlikely to be of clinical importance

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Conflict of interest: ALWP has acted as a consultant to Boots, Zyma, and SmithKline Beecham, which market analgesic drugs, and is a member of the Chemistry, Pharmacy, and Standards Subcommittee of the Committee on Safety of Medicines. The views expressed in the paper are his personal views.

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Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review

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Abstract

Objective: To identify risk factors for operative stroke and death from carotid endarterectomy.

Design: Systematic review of all studies published since 1980 which related risk of stroke and death to various preoperative clinical and angiographic characteristics, including unpublished data on 1729 patients from the European carotid surgery trial.

Main outcome measure: Operative risk of stroke and death.

Results: Thirty six published studies fulfilled our criteria. The effect of 14 potential risk factors was examined. The odds of stroke and death were decreased in patients with ocular ischaemia alone (amaurosis fugax or retinal artery occlusion) compared with those with cerebral transient ischaemic attack or stroke (seven studies; odds ratio 0.49; 95% confidence interval 0.37 to 0.66; $P<0.00001$). The odds were increased in women (seven studies; 1.44; 1.14 to 1.83; $P<0.005$), subjects aged ≥75 years (10 studies; 1.36; 1.09 to 1.71; $P<0.01$), and with systolic blood pressure >180 mm Hg (four studies; 1.82; 1.37 to 2.41; $P<0.0001$), peripheral vascular disease (one study; 2.19; 1.40 to 3.60; $P<0.0005$), occlusion of the contralateral internal carotid artery (14 studies; 1.91; 1.35 to 2.69; $P<0.0001$), stenosis of the ipsilateral internal carotid siphon (five studies; 1.56; 1.03 to 2.36; $P=0.02$), and stenosis of the ipsilateral external carotid artery (one study; 1.61; 1.05 to 2.47; $P=0.03$). Operative risk was not significantly related to presentation with cerebral transient ischaemic attack versus stroke, diabetes, angina, recent myocardial infarction, current cigarette smoking, or plaque surface irregularity at angiography. Multiple regression analysis of data from the European carotid surgery trial identified cerebral versus ocular events at

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ANNEX 16

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CLINICAL TRIALS

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Single-dose dextropropoxyphene in post-operative pain: a quantitative systematic review

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Abstract *Objective*: To determine the analgesic efficacy and adverse effects of single-dose oral dextropropoxyphene alone and in combination with paracetamol for moderate to severe post-operative pain.
Methods: Published reports were identified from a variety of electronic databases including MEDLINE, Biological Abstracts, EMBASE, the Cochrane Library and the Oxford Pain Relief Database. Additional studies were identified from the reference lists of retrieved reports. Summed pain intensity and pain relief data were extracted and converted into dichotomous information to yield the number of patients with at least 50% pain relief. This was used to calculate the relative benefit and number-needed-to-treat for one patient to achieve at least 50% pain relief. Six reports (440 patients) compared dextropropoxyphene with placebo and five (963 patients) compared dextropropoxyphene plus paracetamol 650 mg with placebo.
Results: For a single dose of dextropropoxyphene 65 mg in post-operative pain the number-needed-to-treat for at least 50% pain relief was 7.7 (95% confidence interval 4.6 to 22) when compared with placebo over 4–6 h. For the equivalent dose of dextropropoxyphene in combination with paracetamol 650 mg the number-needed-to-treat was 4.4 (3.5 to 5.6) when compared with placebo. Pooled data showed increased incidence of central nervous system adverse effects for dextropropoxyphene plus paracetamol when compared with placebo. A rank order of single-dose analgesic effectiveness in post-operative pain of moderate to severe intensity obtained from similar systematic reviews is presented.
Conclusion: Dextropropoxyphene 65 mg plus paracetamol 650 mg has a similar analgesic efficacy to that of tramadol 100 mg but with a lower incidence of adverse effects. Ibuprofen 400 mg has a lower (better) number-needed-to-treat than both dextropropoxyphene 65 mg plus paracetamol 650 mg and tramadol 100 mg.

Key words Dextropropoxyphene, Post-operative pain

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Introduction

Dextropropoxyphene is an opioid analgesic which has been widely available since the 1950s. It is commonly found, particularly in combination with paracetamol, under such brand names as co-proxamol and distalgesic. In 1996, there were 10 million prescriptions in England for co-proxamol alone representing one-fifth of all analgesics prescribed (opioid, non-opioid and non-steroidal anti-inflammatory drugs) though it is not clear how much was used for post-operative pain [1].

Patient surveys have shown that post-operative pain is often not managed well [2] and there is a growing need to assess the efficacy and safety of commonly used analgesics as newer treatments become available. Judging relative analgesic efficacy is difficult as clinical trials use a variety of comparators. It can, however, be determined indirectly by comparing analgesics with placebo in similar clinical circumstances to produce a common analgesic descriptor, such as the number-needed-to-treat for at least 50% pain relief.

A reliable method has been developed to convert mean pain outcome values from categorical scales (percentage of maximum possible pain intensity or pain relief %maxSPID and%maxTOTPAR) into dichotomous information (number of patients with at least 50% pain relief) [3–5]. Using this method we have produced a quantitative systematic review of the analgesic efficacy of dextropropoxyphene, both with and without paracetamol, allowing comparison with other analgesics.

Methods

MEDLINE (1966 – November 1996), EMBASE (1980–1996), the Cochrane Library (November 1996), Biological Abstracts (1985–1996), and the Oxford Pain Relief Database (1950–1994) [6] were searched for randomised controlled trials of dextropropoxyphene, and its combinations in post-operative pain. The words 'dextropropoxyphene', 'd-propoxyphene', 'propoxyphene', 'random*', 'clinical trial', 'trial', 'study', 'analgesi*', 'pain' and 41 brand names (including distalgesic and co-proxamol) [7] were used in a broad free-text search without restriction to language. Additional reports were identified from reference lists of retrieved articles and reviews. Unpublished data were not sought.

The inclusion criteria used were: full journal publication, post-operative pain, post-operative oral administration, adult patients, baseline pain of moderate to severe intensity, double-blind design, and random allocation to treatment groups which included dextropropoxyphene and placebo or a combination of dextropropoxyphene plus paracetamol and placebo. Pain outcomes used were total pain relief (TOTPAR) or summed pain intensity difference (SPID) over 4–6 hours or sufficient data provided to allow their calculation. Pain measures which allowed for the calculation of TOTPAR or SPID were a standard five-point pain relief scale (none, slight, moderate, good, complete) or a standard four-point pain intensity scale (none, mild, moderate, severe).

From each study we extracted: the number of patients treated, the mean TOTPAR or mean SPID, study duration, the dose of dextropropoxyphene and paracetamol where appropriate, and information on adverse effects. Mean TOTPAR and mean SPID values were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value [8]. The following equations were used to estimate the proportion of patients achieving at least 50% maxTOTPAR [4, 5]:

$$\text{Proportion with} > 50\%\text{maxTOTPAR} = 1.33 \times \text{mean\%maxTOTPAR} - 11.5 \quad (1)$$

$$\text{Proportion with} > 50\%\text{maxTOTPAR} = 1.36 \times \text{mean\%maxSPID} - 2.3 \quad (2)$$

The proportions were converted to the number of patients achieving at least 50% maxTOTPAR by multiplying by the total number of patients in the treatment group. The number of patients with at least 50% maxTOTPAR was then used to calculate relative benefit and number-needed-to-treat.

Relative benefit and relative risk estimates with 95% confidence intervals were calculated using the fixed effects model [9]. Homogeneity was assumed at $P > 0.1$. A statistically significant benefit of active treatment over placebo was assumed when the lower limit of the 95% confidence interval (CI) of the relative benefit was > 1. A statistically significant benefit of placebo over active treatment was assumed when the upper limit of the 95% CI of the relative benefit was < 1. The number-needed-to-treat and the number-needed-to-harm with 95% CI were calculated [10]. CI includes no benefit of one treatment over the other when the upper limit is represented as infinity.

Dextropropoxyphene is available as either the hydrochloride or napsylate salt. Equivalent molar doses are 65 mg of dextropropoxyphene hydrochloride and 100 mg of dextropropoxyphene napsylate.

Results

A total of 130 published articles were identified. Two could not be obtained and attempts to contact the authors were unsuccessful. Five citations obtained from reference lists of retrieved reports could not be traced by the British Library. Of the 123 retrieved reports 33 were not randomised controlled trials, 24 were not post-operative pain models or included other pain conditions, 21 were not placebo controlled, and in five dextropropoxyphene was used as a rescue analgesic only.

Of the 40 randomised controlled trials that were placebo controlled, patients did not have baseline pain of at least moderate severity in 10 studies, in 16 there were no pain outcomes which were compatible with our inclusion criteria, and two trials were not double-blind. The data from one study was duplicated and therefore one of the duplicates [11] was excluded. Eleven reports met our inclusion criteria and were included in the analysis.

Details of the individual studies, including references for those we could not obtain, are available from the authors or on the World Wide Web (http://www.jr2.ox.ac.uk/Bandolier/painres/dextropr/dextropr.html).

Dextropropoxyphene versus placebo

Six reports compared dextropropoxyphene hydrochloride 65 mg (214 patients) with placebo (226 patients), and one trial also compared a dose of 130 mg (25 patients) with placebo (25 patients). Two trials [12, 13] investigated post-partum pain (episiotomy), one pain following peridontal surgery [14], one post-urogenital surgery [15], one post-gynaecological surgery [16], and one pain after various surgical interventions [17].

The placebo response rate (the proportion of patients experiencing at least 50% pain relief with placebo) varied between 4% and 76%. The dextropropoxyphene response rate (the proportion of patients experiencing at least 50% pain relief with dextropropoxyphene) varied between 19% and 84% (Fig. 1). Data were homogeneous, $P = 0.13$. Dextropropoxyphene 65 mg was significantly different from placebo, relative benefit 1.5 (1.2 to 1.9) (Table 1).

For a single dose of 65 mg dextropropoxyphene, the number-needed-to-treat was 7.7 (4.6 to 22) for at least 50% pain relief over a period of 4–6 h compared with placebo for pain of moderate to severe intensity. One trial [17] used a dose of 130 mg of dextropropoxyphene (25 patients). The relative benefit estimate for dextropropoxyphene 130 mg compared with placebo was 10 (1.4–73). The number-needed-to-treat was 2.8 (1.8–6.5) for at least 50% pain relief over a period of 5 h compared with placebo for pain of moderate to severe intensity.

Adverse effects

Details of adverse effects are given in Table 2. No patients withdrew from the trial as a result of adverse effects, which were all reported to be transient and of mild to moderate severity. One study reported no adverse effects with either placebo or active treatment [12].

In one study the authors reported both dextropropoxyphene 65 mg and 130 mg to have a signifi-

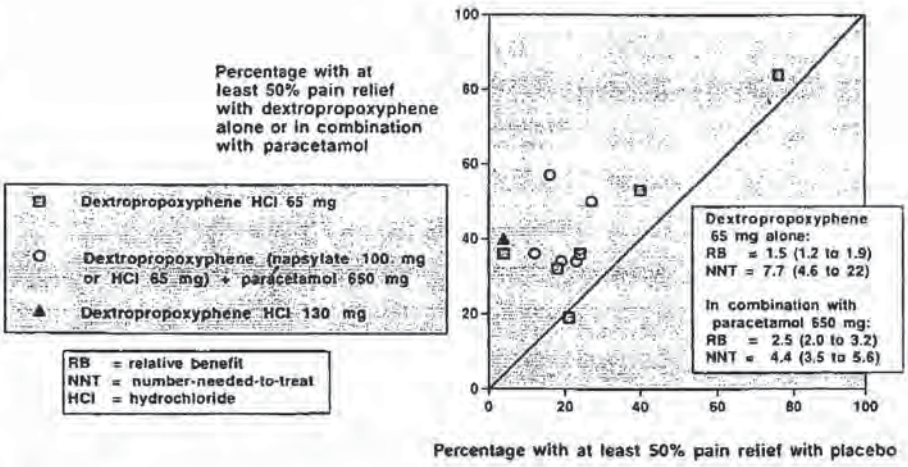

Fig. 1 Dextropropoxyphene or dextropropoxyphene plus paracetamol compared with placebo in randomised controlled trials of single oral doses in patients with moderate or severe postoperative pain for at least 50% pain relief

Table 1 Summary of relative benefit and number-needed-to-treat for trials of dextropropoxyphene and dextropropoxyphene plus paracetamol against placebo. Pooled relative benefit estimates were calculated using the fixed effects model [9]. (*CI* confidence interval)

Number of trials	Dose of dextropropoxyphene	No. of patients with >50% pain relief: dextropropoxyphene	No. of patients with >50% pain relief: placebo	Relative benefit (95% CI)	Number-needed-to-treat (95% CI)
6	65 mg	85/214	60/226	1.5 (1.2 to 1.9)	7.7 (4.6 to 22)
1	130 mg	10/25	1/25	10.0 (1.4 to 73)	2.8 (1.8 to 6.5)
Number of trials	Dose of dextropropoxyphene (plus paracetamol 650 mg)	No. of patients with >50% pain relief: dextropropoxyphene plus paracetamol	No. of patients with >50% pain relief: placebo	Relative benefit (95% CI)	Number-needed-to-treat (95% CI)
5	65 mg hydrochloride or 100 mg napsylate	184/478	74/485	2.5 (2.0 to 3.2)	4.4 (3.5 to 5.6)

cantly higher incidence of grogginess, sleepiness, and light-headedness than placebo ($P = 0.05$) [17]. However, pooled data from the four trials reporting either drowsiness, sleepiness or somnolence [13–15, 17] showed no significant difference in incidence between dextropropoxyphene 65 mg (18/115) and placebo (15/121), with a relative risk of 1.3 (0.7–2.2). No other trial reported light-headedness or grogginess in the dextropropoxyphene group.

Dextropropoxyphene plus paracetamol versus placebo

Four reports compared dextropropoxyphene napsylate 100 mg plus paracetamol 650 mg with placebo, and one used dextropropoxyphene hydrochloride 65 mg plus paracetamol 650 mg. A total of 478 patients received dextropropoxyphene plus paracetamol, and 485 patients received placebo. One report [18] was a meta-analysis of individual patient data from 18 studies with dichotomous information (the number of patients achieving at least 50% maxTOTPAR); eight investigated dextropropoxyphene napsylate 100 mg plus paracetamol 650 mg. Only one of the studies had been published and we excluded the duplicate publication [11]. Two reports [19, 20] studied pain following dental surgery (impacted third molar), two [21, 22] post-orthopaedic surgery, and one [18] pain following both dental and general surgery (abdominal, orthopaedic and gynaecological).

The placebo response rate varied between 6% and 27%. The dextropropoxyphene plus paracetamol response rate varied between 25% and 57% (Fig. 1). The trial results were homogeneous ($P = 0.35$). Dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg was significantly superior to placebo, relative benefit 2.5 (2.0–3.2) (Table 1). For a single dose of dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg the number-needed-to-treat was 4.4 (3.5–5.6) for at least 50% pain relief over 4–6 h compared with placebo for pain of moderate to severe intensity.

Adverse effects

Details of adverse effects are given in Table 2. No patients withdrew from the trial as a result of adverse effects, which were all reported to be transient and of mild to moderate severity. One trial [22] did not give details of adverse effects but reported that there was no significant

Table 2 Summary of adverse effects for trials of dextropropoxyphene and dextropropoxyphene plus paracetamol against placebo. *Pooled relative risk estimates were calculated using the fixed effects* model [9]. (*CI* confidence interval. *N/A* not calculated because no significant difference from placebo was shown for relative risk)

Number of trials	Adverse effect	No. of patients with adverse effects: dextropropoxyphene	No. of patients with adverse effects: placebo	Relative risk (95% CI)	Number-needed-to-harm (95% CI)
3	Nausea	6/101	3/110	2.1 (0.6 to 7.7)	N/A
3	Drowsiness/ sleepiness/ somnolence	18/115	15/121	1.2 (0.7 to 2.2)	N/A
2	Headache	5/75	3/81	1.8 (0.4 to 7.0)	N/A
Number of trials	**Adverse effect**	**No. of patients with adverse effects: dextropropoxyphene plus paracetamol**	**No. of patients with adverse effects: placebo**	**Relative risk (95% CI)**	**Number-needed-to-harm (95% CI)**
3	Nausea	12/405	33/799	0.7 (0.4 to 1.4)	N/A
1	Vomiting	2/323	6/714	1.4 (0.3 to 6.7)	N/A
4	Dizziness	17/428	16/829	2.2 (1.1 to 4.3)	50 (24 to ∞)
3	Drowsiness/ somnolence	57/405	55/799	2.1 (1.5 to 2.9)	14 (9.1 to 30)
4	Headache	14/435	51/829	0.5 (0.3 to 0.9)	−33 (−170 to −19) *

difference between active and placebo groups. The individual patient meta-analysis [18] pooled data on adverse effects from all 18 placebo groups; 714 patients received placebo.

Three studies reported the incidence of drowsiness or somnolence [18–20]. The pooled data indicated a significantly higher incidence in the dextropropoxyphene combination group (57/405) than in the placebo group (55/799), with a relative risk of 2.1 (1.5–2.9) and a number-needed-to-harm of 14 (9.1–30).

Four trials reported dizziness [18–21]. Pooled data indicated a significantly higher incidence of dizziness with dextropropoxyphene plus paracetamol (17/428) compared with placebo (16/829), with a relative risk of 2.2 (1.1–4.3) and number-needed-to-harm of 50 (24–∞).

Four trials reported the incidence of headache [19–22]. The pooled data showed dextropropoxyphene plus paracetamol (14/435) to have a significantly lower incidence of headache than placebo (51/829), with a relative risk of 0.5 (0.3–0.9) and number-needed-to-harm of −33 (−170—19).

Three trials reported the incidence of nausea [18–20]. Pooled data showed no significant difference with dextropropoxyphene plus paracetamol (12/405) than with placebo (33/799), relative risk 0.7 (0.4–1.4).

Vomiting was reported in one study [18]. The incidence of vomiting with dextropropoxyphene plus paracetamol (2/323) was not significantly different from placebo (6/714), relative risk 1.4 (0.3–6.7).

Discussion and conclusions

For a single dose of dextropropoxyphene 65 mg the number-needed-to-treat was 7.7 (4.6–22) for at least 50% pain relief compared with placebo. This means that one in every eight patients with pain of moderate to severe intensity would experience at least 50% pain relief with dextropropoxyphene hydrochloride 65 mg, who would not have done so with placebo. The equivalent number-needed-to-treat for a single dose of dextropropoxyphene (65 mg hydrochloride or 100 mg napsylate) plus paracetamol 650 mg was 4.4 (3.5–5.6), indicating higher efficacy. The CIs of dextropropoxyphene alone and the combination with paracetamol overlapped.

For a single dose of dextropropoxyphene 130 mg, the number-needed-to-treat was 2.8 (1.8–6.5). This appears to show a dose response for dextropropoxyphene. However, given the overlapping CIs and the very small number of patients in the dextropropoxyphene 130 mg trial (50), this conclusion is not robust.

It was surprising that there were so few eligible randomised studies comparing either dextropropoxyphene alone or in combination with paracetamol against placebo, given the fact that 10 million prescriptions were made in 1996 in the UK for combinations with paracetamol. This probably reflects the fact that dextropropoxyphene has long been available, antedating the necessity for intense trial activity associated with the registration of a novel drug.

A rank order of single-dose analgesic efficacy in post-operative pain of moderate to severe intensity is presented in Fig. 2. The additional information came from systematic reviews of single-dose studies in post-operative pain which used a similar method. The only analgesic whose CIs did not overlap the lower limit CI for the dextropropoxyphene plus paracetamol combination was ibuprofen 400 mg, which has a lower (better) number-needed-to-treat. However, as some patients cannot be prescribed non-steroidal anti-inflammatory drugs, it may

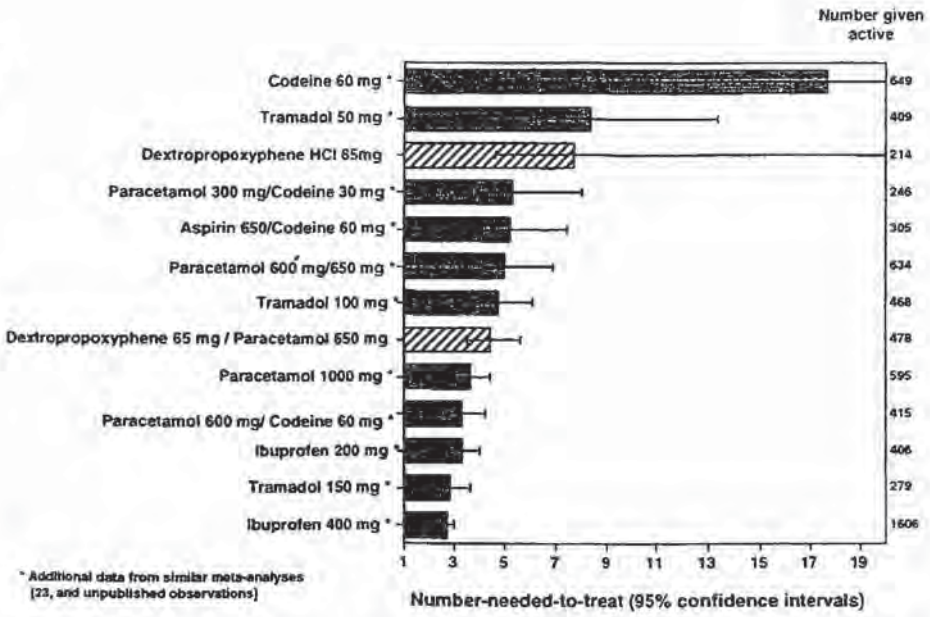

Fig. 2 Numbers-needed-to-treat for single oral doses of analgesics in moderate or severe postoperative pain compared with placebo for at least 50% pain relief

be more appropriate to compare dextropropoxyphene with tramadol. Figure 2 shows the dextropropoxyphene-plus-paracetamol combination to have a slightly lower number-needed-to-treat than tramadol 100 mg, although the CIs overlap substantially.

A single dose of dextropropoxyphene 65 mg plus paracetamol 650 mg showed a significantly higher incidence of central nervous system adverse effects (somnolence, dizziness) than placebo (Table 2). These adverse effects have also been shown for tramadol 100 mg with a lower (worse) number-needed-to-harm for both dizziness and somnolence [18]. Tramadol 100 mg also showed a significantly higher incidence of nausea and vomiting than placebo. These adverse effects were reported with dextropropoxyphene 65 mg plus paracetamol 650 mg but the incidence was not significantly different from placebo.

The combination of dextropropoxyphene 65 mg with paracetamol 650 mg showed similar efficacy to tramadol 100 mg for single-dose studies in post-operative pain with a lower incidence of adverse effects.

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ANNEX 17

assume that this rate of screening is typical for people with learning disability.

Breast cancer is the second most common cancer in women, and nulliparity increases the risk for women over 40.[1] Older women with Down's syndrome and with learning disability in general are a vulnerable group. A study of the association between cancers and mental handicap showed an increase in deaths from cancer over the past five decades: of 34 women in that study who died of cancer, five had breast cancer.[2]

The importance of health education for carers and for people with learning disability and of good health screening programmes has recently been highlighted by the Department of Health.

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Co-proxamol is effective in chronic pain

EDITOR—Li Wan Po and Zhang's review substantiates the widely held view that paracetamol is as effective as co-proxamol in single dose for acute pain.[1] We agree with their message; indeed, another recent systematic review comes to the same conclusion.[2]

The authors dismiss comments we have made about the use of co-proxamol.[3] However, our remarks related to the treatment of chronic pain, which cannot and should not be managed with single doses of analgesics. Co-proxamol is recommended and has been extensively used at step 2 of the World Health Organisation analgesic ladder for managing chronic pain in cancer, when it is used in repeated doses. We are concerned that Li Wan Po and Zhang fail to make sufficiently clear that their analysis was of single dose studies only. It may therefore be taken out of context and dissuade doctors from implementing this good practice.

As we and others have suggested, the analgesic efficacy of single and repeated doses of co-proxamol is likely to differ, a lesson learnt 20 years ago with other morphine-like opioid analgesics.[4] Because of the extensive first pass metabolism of dextropropoxyphene, which is dose dependent,[5] plasma concentrations after a single dose may be four times lower than those found in steady state after regular six hourly administration. In addition, the active metabolite, norpropoxyphene, has a longer elimination half life than the parent compound and will accumulate to some extent on regular dosing. Thus there is a strong pharmacokinetic basis for believing that repeated doses of co-proxamol are likely to be more effective than single doses.

Li Wan Po and Zhang's systematic review is therefore not directly relevant to the discussion of the efficacy of co-proxamol as it is usually used—in repeated doses. We agree that there is a lack of data from randomised controlled trials relevant to this situation. Such trials are required to settle the argument but are difficult to accomplish. In the absence of this evidence we abide by our view that extensive anecdotal experience cannot be disregarded. It is worth listening to patients when they report that pain not controlled by regular paracetamol alone is relieved by repeated doses of co-proxamol.

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Mefloquine to prevent malaria

Interpretation of study was not based on evidence

EDITOR—Croft and Garner's interpretation of their systematic review of controlled studies involving mefloquine cannot qualify as evidence based.[1] They have selected two outcome measures, non-compliance and withdrawal, as proxy markers for drug tolerance without any evidence of correlation of this behaviour to tolerability. In Ohrt's study,[2] which makes up 43% of the mefloquine group withdrawals, four of the seven withdrawals were because soldiers were redeployed and the remaining three were because of protocol failures[2] and concurrent fever, none of which was obviously related to tolerability. In clinical studies where subjects were at no risk of malaria the threshold and reason for withdrawal from prophylaxis may be different from those of travellers, whom the authors claim will behave similarly despite a different risk of malaria.

The author's argument that a symptom based outcome is less objective than a withdrawal based outcome when measuring tolerability is subjective. The claim that poor compliance or withdrawal from mefloquine is more likely to leave travellers incompletely protected compared with other regimens is unsupported and selectively used to discredit mefloquine. Their study and others' confirm that mefloquine is an effective antimalarial prophylactic drug. To restrict its use to the fittest and healthiest travellers on the basis of differences in undefined withdrawal rates in non-travellers because no current studies define its true tolerability is naive.

An important issue, which the authors have failed to acknowledge, is that the tolerability of any prophylactic regimen needs to be counterbalanced by the risks of morbidity and mortality associated with the disease it is used against. Under the banner of an evidence based analysis the authors have used a limited dataset, which is arguably inadequate for meta-analysis, to reflect their personal preferences on the indications for mefloquine prophylaxis.

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Withdrawal rates are misleading measure of tolerability

EDITOR—Croft and Garner[1] draw conclusions about the tolerability of mefloquine for malaria prophylaxis that are not justified. Based on a meta-analysis of "withdrawal rates, presumably from side effects" from randomised trials they conclude that "mefloquine prophylaxis may be less effective than alternative chemoprophylaxis that is better tolerated."

Firstly, higher withdrawal rates with mefloquine occurred only in comparison to placebo, not in comparison to alternative chemoprophylaxis such as doxycycline or chloroquine and proguanil. Secondly, the use of withdrawal rates is a problematic measure of tolerability because the reasons for withdrawal from controlled trials are often unrelated to the study drug. For example, in Ohrt et al's trial, which contributed a considerable proportion of the weight in the analysis, 10 out of 16 withdrawals were due to travel from the study area. The authors clearly stated that "no participant was withdrawn from the study because of intolerance to the study drugs or adverse effects that seemed to be related to the study drugs."[2] It is misleading to use withdrawal rates as a direct measure of tolerability without considering the reasons that led participants to abandon the study.

Non-immune visitors to malarious areas need to know about the risk associated with malaria. Only with this in mind will they be able to make informed choices when they experience adverse events from prophylactic drugs. Adequate advice before travel on malaria prophylaxis should also include the following messages:

ANNEX 18

Letters

Co-proxamol and suicide

Licence needs to be changed

EDITOR—We agree with Hawton et al that co-proxamol presents a major overdose hazard, their results illustrating the difficulties for licensing authorities in limiting availability of prescription medicines that are only hazardous in overdose.[1]

Co-proxamol is more likely to result in death; it causes prolongation of the QRS interval in an electrocardiogram in experimental animals and in humans.[2,3] This property is usually associated with sodium channel blockade and is a precursor to ventricular arrhythmia. We have shown a significant relation between estimated dextropropoxyphene dose (based on paracetamol concentration) and QRS prolongation in a case of co-proxamol poisoning,[4] an effect not seen with other opioid combination products.

Dextropropoxyphene is rapidly absorbed from the gastrointestinal tract, increasing early cardiac risk, with death happening within one hour after ingestion.[5] Most patients probably die of co-proxamol poisoning as a result of its combined cardiac (non-opioid) and central nervous system (opioid) effects before hospital admission. Understanding these factors may also improve acute care.

Prescribing patterns for co-proxamol may show geographical variation, which could alter the risk estimates calculated by Hawton et al. In Edinburgh co-proxamol poisoning accounted for 4.8% of 5583 patients admitted with self harm in the two years from July 2000 to June 2002 (overall 20% of patients took an opioid). These figures seem similar to those of Hawton et al.

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Competing interests: None declared.

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Co-proxamol should be restricted, not banned

EDITOR—Smith suggests that co-proxamol be banned.[1] I am surprised by this reaction to Hawton et al's paper on co-proxamol and suicide.[2] Hawton et al clearly advocate restricting the availability of co-proxamol.

Dextropropoxyphene is closely related to methadone, and like methadone it has noradrenergic analgesic properties in addition to its opioid effect. Patients who attend pain clinics have often tried several compound analgesics, and occasionally they report that co-proxamol is the most effective. This may reflect a neuropathic component to their pain that is quite different to the postoperative pain for which co-proxamol is no better than paracetamol alone.

The evidence suggests that co-proxamol should be restricted perhaps to specialist use but not banned outright. After all a knee jerk ban of thalidomide would have deprived medicine of a drug still used in the treatment of leprosy.

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Competing interests: None declared.

1 Smith R. Choice: Unknown unknowns in suicide and depression. *BMJ* 2003;326 (7397):0. (10 May.)
2 Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. *BMJ* 2003;326:1006-8. (10 May.)

Availability of co-proxamol has been successfully reduced in Doncaster

EDITOR—In 1998 an audit of suicides in Doncaster identified the alarming rate of co-proxamol overdose as a method of suicide: of the 44 suicides with prescribed drugs between 1995 and 1998, 18 were with co-proxamol (41%).[1] That this is much higher than the national figure of 18% quoted by Hawton et al[2] may be because the rates of prescribing of co-proxamol in Doncaster (around 11 million tablets a year) were 65% higher than the national average.

Hawton et al recommend restricting co-proxamol on the evidence that restricting availability of a specific means of suicide can reduce deaths. Doncaster Health Authority reached the same conclusion in 1998 and undertook to reduce the amount of co-proxamol in circulation by asking general practitioners to be more cautious in prescribing the drug. Doncaster Royal Infirmary also removed co-proxamol from its formulary.

The table shows how, four years on, the policy of reducing prescribing has been successfully implemented: around 60% fewer tablets are currently prescribed than in the period up to 1998 and the prescribing rate is now lower than the national average.

The numbers of suicides among Doncaster residents, also shown in the table, are too small for us to show any relation between the amount of co-proxamol prescribed and the number of suicides with the drug or the total number of suicides. However, we cannot help but be encouraged by the numbers: only five since the beginning of 2000.

The remarkably low number of suicides in 2002 is not a final figure, but many more are unlikely to emerge, and this clearly cannot be attributed to reductions in co-proxamol prescribing. We can, however, be sure that the quantity of tablets in circulation has been massively reduced and that the evidence, as quoted by Hawton et al, implies that this is likely to reduce deaths.

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1 Sims A. *Doncaster suicide audit.* Doncaster: Doncaster Health Authority, 1998.
2 Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. *BMJ* 2003;326:1006-8. (10 May.)

Effectiveness of reducing prescriptions of co-proxamol in Doncaster

	1996	1997	1998	1999	2000	2001	2002
No of co-proxamol tablets per prescribing unit*:							
Doncaster	27.9	28.0	26.7	17.6	13.1	11.7	10.7
England and Wales	16.9	16.7	16.4	15.9	15.1	14.5	13.8
No of suicides†:							
With co-proxamol	5	3	7	5	2	3	0
All other methods	25	29	36	22	31	26	14

*Based on data from the Prescription Pricing Authority for preceding eight months for 1996 and on first six months only for 2002.
†Office for National Statistics public health mortality file; data for 2002 not final.

ANNEX 19

CO-PROXAMOL OR PARACETAMOL FOR ACUTE PAIN?

BNF 4.7.1

Fifteen years ago, we drew attention to the widespread use of the fixed-dose combination product co-proxamol (dextropropoxyphene 32.5mg plus paracetamol 325mg) and the paucity of evidence that it was more effective than paracetamol alone.[1] Co-proxamol is still widely used in the UK. Here, we consider its use and review data comparing co-proxamol with paracetamol in the short-term relief of pain.

USE OF CO-PROXAMOL

In a recent survey of 30 teaching hospitals, 35% of prescriptions for paracetamol-containing analgesics were for co-proxamol.[2] The survey gives no details on how the combination was used (e.g. whether in single or multiple doses, or 'as required'), except that in one of the largest hospitals it was used mainly for acute pain. The reason for the widespread use of co-proxamol is unclear but one explanation is a belief that it is more effective than the individual drugs given alone.

ANALGESIC EFFECT

Data from randomised controlled trials were assessed in a systematic review to evaluate whether dextropropoxyphene hydrochloride (65mg or 100mg) in combination with paracetamol 650mg was more effective than paracetamol 650mg alone.[3] The authors analysed pooled data from 24 single-dose randomised controlled trials involving a total of 2097 patients with postpartum or orthopaedic pain, or with pain following tooth extraction, episiotomy, caesarean section or other (unspecified) surgery. The outcome measures used for comparing effectiveness of the treatments were: difference in pain intensity over 4–6 hours (12 hours in one study); and response rate ratio (the proportion of patients reporting at least moderate pain relief in the treatment group relative to the control group). Since most of the single-dose trials compared either the combination or paracetamol with placebo rather than comparing the two treatments directly, the authors performed two independent sub-meta-analyses. In one of these, the efficacy of the combination was compared with that of paracetamol using data from direct comparison trials only (3 trials, involving 301 patients). In the other, the two treatments were compared indirectly using data from the placebo-controlled trials. In the direct comparison trials, the effects of the combination and paracetamol 650mg on pain intensity, or on response rate ratio, were not statistically different. The indirect comparisons showed that both the combination and paracetamol were significantly better than placebo, but again there was no difference between the combination and paracetamol. There was also no difference between the two treatments in the rates of unwanted effects.

Another published systematic review analysing data from indirect comparisons similarly found no significant difference between single-dose dextropropoxyphene plus paracetamol and paracetamol alone used to treat post-operative pain.[4]

COST

A single dose of co-proxamol (2 tablets containing a total of 650mg paracetamol) costs about 2p compared with about 1p for paracetamol at the more usual single dose of 1g.

CONCLUSION

There is no evidence that dextropropoxyphene 62.5mg or 100mg in combination with paracetamol 650mg, given as a single dose, is more effective than paracetamol 650mg alone in relieving acute pain such as that occurring postpartum or after orthopaedic surgery, tooth extraction, episiotomy or caesarean section. Co-proxamol (dextropropoxyphene plus paracetamol) costs twice as much as paracetamol and has the disadvantage that the individual constituents are not obvious from the name. We continue to believe that for acute pain co-proxamol should be replaced by paracetamol alone. The position for prolonged use is not yet so clear.

[M=meta-analysis; R=randomised controlled trial]

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ANNEX 20

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Population impact of strategies designed to reduce peptic ulcer risks associated with NSAID use

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SUMMARY *The risk of ulcer complications rises steeply with dose for aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) but estimates of the overall incidence of bleeding ulcer are unreliable. Drug utilisation data, epidemiological data on the frequency of bleeding ulcer and death, and the relative risks associated with different NSAIDs, indicate that the number of cases of bleeding ulcer attributable to NSAIDs in the United Kingdom is approximately 2,400. Substitution of ibuprofen at a dose of 2.4 g/day for all other NSAIDs would reduce the number of events attributable to NSAIDs from 2,431 to 695 annually. At a dose of 1200 mg/day, substituting ibuprofen or another safe NSAID would be likely to reduce events to zero. Similarly, substitution of ibuprofen 2.4 g/day for all other NSAIDs would reduce attributable ulcer mortality to 80. The total number of excess cases attributable to aspirin is 753 annually. If prophylactic aspirin was prescribed solely at a dose of 75 mg/day, the number of cases would fall to 445 annually and the number of related deaths from 87 to 51 annually. NSAIDs and aspirin account for approximately one-third and previous ulcer for about one-fifth of the overall risk of bleeding ulcer and its complications.*

Current evidence indicates clearly that the risk of ulcer complications rises steeply with dose for both non-aspirin non-steroidal anti-inflammatory drugs (non-aspirin NSAIDs) and aspirin. There is also no intrinsic reason for believing that these risks differ materially for any of the non-aspirin NSAIDs.

Incidence of bleeding ulcer

Estimates of the overall incidence of bleeding ulcer are unreliable. In the United States, it is estimated that ulcer complications are the primary cause of approximately 6,500 deaths annually but 16,500 ulcer-related deaths have been claimed to be associated with NSAID use. By contrast, there are believed to be approximately 3,500 deaths associated with bleeding ulcer in the United Kingdom, whether or not they are associated with NSAID use. Since the UK population is about one quarter of that in the US, these figures are inconsistent.

For a reliable estimate of the risk of bleeding ulcer associated with and caused by NSAIDs, it is necessary to know the proportion of cases who use NSAIDs, the overall annual frequency of bleeding ulcer and death, and the relative risks of different NSAIDs. Data on the risk of bleeding ulcer (but not ulcer perforation) associated with NSAID use for the UK were published in 1994.[1] Among 1,121 patients aged over 60 admitted with ulcer bleeding in five cities in the UK, 411 were taking NSAIDs.[2] The proportionate use of NSAIDs, and the odds ratios for ulcer bleeding, are listed in Table 1; these figures are broadly consistent with clinical experience, though the odds ratios for piroxicam and indomethacin are higher than reported elsewhere. (Applying these data to the UK population assumes that the case control study is a reliable estimate of the pattern of drug use among patients with bleeding ulcer.)

The total number of cases of bleeding ulcers (of any cause) in the UK is provided by a

Table 1. Use of NSAIDs and relative risk of admission for ulcer bleeding in patients aged over 60 (n=1,121) in the UK[1]

NSAID	No of cases using NSAID	Odds ratio	$CI_{95\%}$
Diclofenac	71	4.2	2.6–6.8
Ibuprofen	88	2.0	0.4–2.8
Indomethacin	57	11.3	6.3–20.3
Naproxen	90	9.1	5.5–15.1
Piroxicam	57	13.7	7.1–26.3
Any NSAID	411	4.5	3.6–5.6

Table 2. Estimate of cases for ulcer bleeding attributable to NSAIDs in patients aged over 60

NSAID	Estimate of no of cases in UK per year in patients taking NSAID*	Odds ratio for ulcer bleeding ($CI_{95\%}$)*	Estimate of no of cases attributable to NSAID**
Diclofenac	540	4.2 (2.6, 6.8)	411
Ibuprofen	669	2.0 (0.4, 2.8)	334
Indomethacin	434	11.3 (6.3, 20.3)	396
Naproxen	685	9.1 (5.5, 15.1)	610
Piroxicam	434	13.7 (7.1, 26.3)	402
Any NSAID	3,126	4.5 (3.6, 5.6)	2,431

*Reference 1. **Reference 2.

study in a population of approximately 3.5 million people aged 60 or over, in which there were 894 cases and 102 deaths over a period of 4 months.[2] Extrapolating this to the population of approximately 11 million people aged 60 or older in the UK puts the annual number of cases at 8,528 and the annual number of deaths at 981.

The number of cases attributable to NSAID use in the UK can be calculated by estimating the total number of cases among people using NSAIDs from the five cities study (whether or not the NSAID caused the event) (second column of Table 2); dividing this by the respective odds ratios provides the number of cases expected in that number of people; the remainder is the excess of cases attributable to the NSAID (column four). These figures suggest that the number of cases attributable to NSAIDs is approximately 2,400 of the total of 8,500 occurring annually.[3]

Using these data, it is possible to estimate the reduction in morbidity of substituting safer NSAIDs for those associated with higher risk. For example, substitution of ibuprofen at a dose of 2.4 g/day for all other NSAIDs would reduce the number of events attributable to NSAIDs from 2,431 to 695 annually. At a dose of 1200 mg/day, substituting ibuprofen or another safe NSAID would be likely to reduce events to zero.

The same approach can be used to estimate mortality (Table 3). These figures suggest that 280 of the 360 deaths annually in this group of patients are due to NSAIDs. Substitution of ibuprofen 2.4 g/day for all other NSAIDs would again be likely to reduce this figure to 80; there would also be no deaths expected with substitution of ibuprofen at a dose of 1200 mg/day.

Table 3 reproduced with permission from John Wiley & Sons Ltd (Pharmacoepidemiol Drug Safety 2001; 10: 13–19)

Table 3. Estimates of deaths following admission for ulcer bleeding in people aged 60 or over associated with NSAID use in the UK[3]

NSAID	Calculated	Expected	Excess
Diclofenac	62	15	47
Ibuprofen	77	39	38
Indomethacin	50	4	46
Naproxen	79	9	70
Piroxicam	50	4	46
Any NSAID	360	80	280

Impact of indication on risk

These estimates of risk apply to the use of NSAIDs in the community, most of which is for chronic or intermittent treatment. Other patterns of use may be associated with different risks — for example, the short-term use of indomethacin or azapropazone for gout or the use of NSAIDs for postoperative pain. These risks have been poorly characterised in the past.

The acute safety of NSAIDs was addressed in a study comparing the risk of gastrointestinal bleeding associated with postoperative treatment with ketorolac, diclofenac or ketoprofen.[4] None of 5,634 patients treated with ketorolac developed gastrointestinal bleeding; there was one case in 2,568 patients treated with diclofenac and three in 3,043 patients given ketoprofen. There was no significant difference in risk between these drugs and none of these patients died.

Risks associated with low-dose aspirin

Low-dose aspirin (75–300 mg/day) is widely prescribed as prophylaxis against cardiovascular events. Even at these doses, it is associated with a greater risk of ulcer bleeding and this risk may be further increased by concurrent use of NSAIDs and other factors.

The odds ratio for hospital admission for ulcer bleeding in patients over 60 years taking low-dose aspirin increases from 2.3 at 75 mg/day to 3.2 at 150 mg/day and 3.9 at 300 mg/day.[5] Applying the methodology described above, the total number of excess cases attributable to aspirin is 753 annually (Table 4). If prophylactic aspirin was prescribed solely at a dose of 75 mg/day, the number of cases would fall to 445 annually and the number of related deaths from 87 to 51 annually. In this context, note that a published meta-analysis suggesting that the risk associated with prophylactic aspirin is not dose-related may have flaws due to inappropriate case comparisons.[6]

Other factors increase the risk of complications. Concurrent use of NSAIDs increases the risk substantially (Table 4); additional independent risk factors identified in the five cities study are listed in Table 5.[6] The importance of the excess risk associated with diabetes and heart failure is uncertain: these associations were unexpected and may have been a statistical anomaly, or may be due to the effects of chronic disease on local blood supply and tissue nourishment. No data were available on the possible risks associated with selective serotonin reuptake inhibitors.

It is difficult to translate the odds ratio into a figure that meaningfully conveys the degree of risk faced by individual patients. It is, however, useful to estimate the proportionate risk attributable to each factor (Table 6). The use of NSAIDs and aspirin accounts for approximately one-third and previous ulcer for about one-fifth of the overall risk. Although the absolute risk associated with smoking is low, the high prevalence of smokers means that it accounts for 10% of the overall risk. The total contribution of the known risks amounts to approximately 80% of the overall risk, which suggests that the risk associated with other factors, including *Helicobacter pylori*, may be relatively small.[7]

Table 4 reproduced with permission from John Wiley & Sons Ltd (Pharmacoepidemiol Drug Safety 2001; 10: 13–19)

Table 4. Estimate of cases for ulcer bleeding attributable to prophylactic aspirin in patients aged over 60[3]

Dose (mg/day)	Estimate of no of cases in UK per year in patients taking low-dose aspirin*	Odds ratio for ulcer bleeding ($CI_{95\%}$)**	Estimate of no of cases attributable to aspirin†
Daily aspirin for 1 month or longer			
75	205	2.3	116
150	167	3.2	115
300	472	3.9	351
Other doses	251	–	171
Daily aspirin for less than 1 month			
Any dose	319	9.2	284
Daily aspirin concurrent with other NSAID			
Any dose	350	9.8	312

*Reference 1. **Reference 5. †Reference 3.

Table 5. Significant accessory risk factors compared with community controls[6]

	Odds ratio	$CI_{95\%}$
Anticoagulants	7.8	2.8–21.5
Heart failure	5.9	2.3–13.1
Previous ulcer	3.8	2.6–4.9
Diabetes	3.1	1.2–4.3
Corticosteroids	2.7	1.3–4.5
Smoking	1.6	1.2–2.0

Table 6. Attributable risk associated with individual risk factors[6]

NSAID/aspirin use	33%
Prior ulcer	19%
Smoking	10%
Heart failure	5%
Diabetes	4%
Corticosteroids	3%
Total	77%

Summary

All non-selective NSAIDs are associated with an increased risk of adverse gastrointestinal events, particularly affecting the upper gastrointestinal tract. These effects are dose-related. Very short duration use may not pose a clinical problem, at least postoperatively, but during chronic use in the community other independent risk factors greatly increase the risks associated with NSAIDs. Prophylaxis with aspirin confers substantial protection against cardiovascular events but requires only low doses. However, aspirin is associated with an increased risk even at a dose of 75 mg/day, and this risk is magnified by accessory factors and the use of other NSAIDs. These data emphasise the importance of choosing the least toxic NSAID at the lowest effective dose for patients with rheumatic disease.

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ANNEX 21

MEDICAL PRACTICE

Contemporary Themes

Effect of restrictions on prescribing patterns for dextropropoxyphene

GILLIAN M SHENFIELD, A N JONES, J W PATERSON

Summary and conclusions

Prescribing of compound analgesics containing dextropropoxyphene was limited to consultants only in a teaching hospital. Inpatient prescribing (mainly by junior staff) fell immediately to very low levels but outpatient prescribing (by consultants) fell more slowly to about one-third of the original level, suggesting that patients and doctors find dextropropoxyphene compounds useful. Prescriptions for paracetamol increased but so did those for other compound analgesics, particularly those containing high doses of codeine, indicating a belief that compound analgesics have a role in treatment. Restrictions may produce unexpected results and monitoring is essential, but the method of audit used by pharmacies is not suitable for detailed analysis.

Introduction

Dextropropoxyphene, structurally related to the narcotic analgesic methadone, has become one of the most popular analgesics in the world, especially in combination with paracetamol. Recently its widespread use has caused concern.[1]

Reports from Britain,[2 3] the United States,[4–6] and Denmark[7] have shown that overdose of dextropropoxyphene can rapidly cause death from respiratory failure. In addition the paracetamol in combined preparations may cause death from hepatic failure, and in Britain, between 1970 and 1974, 28% of deaths from paracetamol poisoning were due to a dextropropoxyphene/paracetamol combination.[8] The toxicity of dextropropoxyphene may also be enhanced by alcohol,[6 7 9 10] and death has been reported from ingestion of only 15 tablets in combination with alcohol.[5] There is some evidence that dextropropoxyphene has addictive properties.[8 11–14]

Formal clinical trials suggest that it has low potency as an analgesic. Fifteen double-blind trials showed that codeine in lower or equal doses produced analgesia equal to or greater than dextropropoxyphene, and seven studies showed that aspirin and caffeine in various doses were of equal or greater efficacy.[15] In nine studies dextropropoxyphene was more effective than placebo but in another seven it was not.[15] A later study[16] found that it had less analgesic effect than aspirin or paracetamol alone. Despite this the combination of dextropropoxyphene and paracetamol remains extremely popular.

Australia is no exception to world trends, and "Digesic" (dextropropoxyphene hydrochloride 32·5 mg and paracetamol 325 mg, Dista) is one of the most widely prescribed analgesics. For the reasons outlined above, on 1 March 1978 prescribing restrictions were introduced in our 517-bed teaching hospital. From that date combination products containing dextropropoxyphene could be prescribed only by consultants. We describe the results of these restrictions.

Methods

The pharmacy keeps records of numbers of tablets purchased in any given period. These figures were collected for the nine-month period before and after the introduction of restrictions for the following commonly prescribed analgesic tablets: dextropropoxyphene hydrochloride 32·5 mg/paracetamol 325 mg (Digesic); dextropropoxyphene napsylate 100 mg≡65 mg hydrochloride (Doloxene); paracetamol

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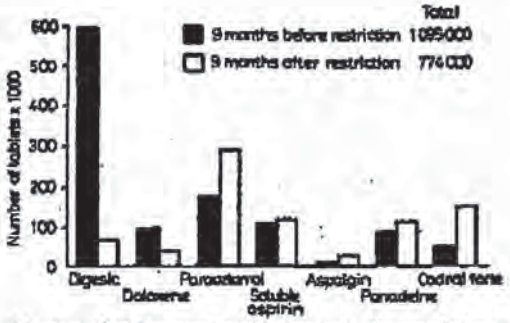
500 mg; soluble aspirin 300 mg; aspirin 300 mg/codeine 8 mg (Aspalgin); paracetamol 500 mg/codeine 8 mg (Panadeine); and aspirin 225 mg/paracetamol 150 mg/codeine 30 mg (Codral Forte). The actual numbers of tablets prescribed were not available, but note was made of the quantities of Digesic *supplied* to outpatients (90 000 patients a year) and inpatients (17 000 patients a year).

Results

The figure shows the numbers of tablets purchased before and after restrictions, and table I shows the individual tablets expressed as percentage of total analgesics purchased. Table II shows total outpatient and inpatient supplies of Digesic for the nine months before and after restrictions.



Number of tablets purchased before and after restrictions.

TABLE I—*Tablets expressed as percentage of total analgesics purchased*

	Before restriction	After restriction
Dextropropoxyphene hydrochloride/paracetamol (Digesic) ..	54·8	8·4
Dextropropoxyphenenapsylate hydrochloride (Dolosene) ..	8·7	4·5
Paracetamol	15·5	38·5
Soluble aspirin	9·6	14·9
Aspirin/codeine (Aspalgin) ..	1·0	2·5
Paracetamol/codeine (Panadeine)	6·8	24·1
Aspirin/paracetamol/codeine (Codral Forte)	3·6	18·1

TABLE II—*Number of tablets of Digesic supplied in hospital*

	Outpatients	Inpatients
Before restrictions imposed		
July–September 1977	150 000	40 000
October–December 1977	190 000	52 000
January–March 1978	110 000	36 000
After restrictions imposed		
April–June 1978	75 000	<1 000
July–September 1978	25 000	<1 000
October–December 1978	45 000	<1 000

The total number of analgesic tablets purchased over a nine-month period fell from 1·095 million to 0·774 million.

The use of Digesic in inpatients fell dramatically, but there was a slower decline in outpatient use. Prescribing of paracetamol increased by about half but that of soluble aspirin did not change. The use of compound analgesics, particularly Codral Forte, increased and since Codral Forte is very expensive the total cost of drugs fell proportionately less than the total number purchased—from A$13 375 to A$11 525 (table III).

Some problems arose from using purchasing and supply figures to estimate drug usage. Tables II and III show that a total of 578 000 Digesic tablets were supplied before restrictions to outpatients and inpatients combined, but the total number of tablets purchased in the relevant period was 600 000. Similarly, after the restrictions 148 000 tablets were supplied to both outpatients and inpatients and yet only 65 000 were purchased. Thus a greater or lesser effect of the prescribing restriction could be deduced depending whether purchase data or supply data were used.

The purchasing figure for a further nine months from January to September 1979, during which restrictions persisted, were therefore examined (table III). They showed that the total number of tablets had increased again from 774 000 to 854 000. Accompanying this was a rise in drug costs for analgesics, the new nine-month total being A$13 966. The reduction in amounts of Digesic and Dolosene purchased was largely balanced by increases in the amounts of paracetamol (Panadeine) and Codral Forte (table III).

TABLE III—*Analgesic purchases over three nine-month periods*

	July 1977–Mar 1978	April–Dec 1978	Jan–Sep 1979
Overall total	1 095 000	774 000	854 000
Total cost	$13 375	$11 525	$13 966
Dextropropoxyphene hydrochloride/paracetamol (Digesic)	600 000	65 000	150 000
Dextropropoxyphene-napsylate/hydrochloride (Dolosene)	95 000	48 000	48 000
Paracetamol	169 000	286 000	258 000
Paracetamol/codeine (Panadeine)	74 000	168 000	120 000
Aspirin/paracetamol/codeine (Codral Forte)	40 000	140 000	178 000

Discussion

These results indicate that restricting the prescribing of a particular drug to consultants may have a substantial effect on prescribing patterns. The changes observed, however, raise important questions about the reasons for prescribing a particular drug, the wisdom of imposing restrictions, the importance of monitoring changes, and the methods of assessment to be used.

Our data are based on numbers of tablets purchased, since this is how our pharmacy does its auditing; and even had there been large stocks of Digesic at the time restrictions were imposed the figures for the third nine-month period we monitored suggest that there had been a true drop in the amount prescribed. Some outpatients, however, finding that they were not being given Digesic at the hospital, may have obtained prescriptions from their general practitioners.

Departments of pharmacy normally audit drug usage in terms of money spent and the acquisition of drugs. Inventory control centres on compliance with audit requirements rather than establishing an active record of the dispersement of drugs for ward units or doctors, and changes in drug usage cannot be identified quickly and accurately. We had not been fully aware of this difficulty before performing the present analysis.

Figures were available for the supply of Digesic to inpatient and outpatient departments. Inpatient prescribing of Digesic, predominately by junior staff, fell immediately. Of more interest is the lesser decline in outpatient, predominately consultant, prescribing. This suggests that some patients and experienced doctors believe that Digesic is a useful drug not readily substituted by any other product. Since the evidence for its analgesic properties is limited, its central effects may possibly be responsible for its popularity. Miller[10] stated "it appears that factors other than intrinsic therapeutic value are responsible for the commercial success of propoxyphene." Digesic is marketed as an attractive, compact, oblong white tablet that is easily swallowed. In Australia, in 1978-9, prescriptions were written on pharmaceutical benefits for 2 346 840 tablets of Digesic. Prescribing numbers for another preparation (Capadex) with identical constituents but marketed as a green and yellow capsule were only 244 820. The popularity of Digesic may therefore be related to expert marketing techniques.

Our findings also indicate a definite tendency to prescribe compound analgesics. We were greatly concerned to see that a compound containing 30 mg of codeine phosphate (and pre-

scribed two at a time) had become the compound analgesic of first choice. It is arguable that this could do more harm than the dextropropoxyphene it has replaced since codeine is well known to cause constipation, and this may be particularly dangerous in surgical wards. Of special concern is that this tendency to use the compound analgesics, in particular Codral Forte, became even more pronounced with longer follow-up.

We achieved our aim of reducing the use of Digesic within the hospital but created other problems. Our results show that prescribing restrictions are not the answer to the misuse and overuse of drugs. If they are introduced they should be carefully monitored by methods more subtle than the hospital pharmacy audit. At best they will only provide a short-term solution, and only by a continuous programme of active education of medical students and practising doctors will prescribing habits be improved.

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Hospital Topics

Hospital work load produced by breast-cancer screening programme run by trained non-medical staff

W D GEORGE, R A SELLWOOD, D A ASBURY, G HARTLEY

Summary and conclusions

In a feasibility study of mass population screening for breast cancer by annual clinical examination and mammography the findings of non-medical staff (nurses and radiographers) were used to estimate the hospital work load generated by such a programme. Among 2490 women who attended for the first time by invitation the rate of referral for a surgical opinion based on the findings of the non-medical staff was 7·9% and the biopsy rate 2·5%. In the second and third years referral rates fell to 4·3% and 2·7% respectively and the biopsy rates to 1·1% and 1·4%.

The rates of referral and biopsy among 1203 women who referred themselves for screening were higher, but many self-referred women were symptomatic; those without symptoms had rates of referral and biopsy similar to those of the invited women.

Extrapolation of these findings to a population of 200 000 in a typical health district showed that the hospital work load would be high in the first year of screening with 44 outpatient referrals per week and 14 biopsies. By the third year, however, only seven referrals and four biopsies a week could be expected. The work load would be reduced by a third if screening were confined to women over the age of 50.

Introduction

The results of previous studies suggest that screening for cancer of the breast by annual clinical examination and mammography leads to detection of the disease at an early stage and consequently to improved survival.[1]

With present resources of medical manpower it would be impossible to offer a screening service to all women at risk unless examinations were carried out by trained non-medical staff. Such a service would require access to a hospital outpatient clinic to which patients with abnormalities could be referred for consultation and treatment. This might increase the surgical work load significantly and the size of the increase might be a major factor in determining the feasibility of providing a screening service.

In previous studies the rate of biopsy has ranged from 0·38%[2] to 9·8%[3] and the rate of detection of cancer from 1·5 per 1000[2] to 24·6 per 1000.[4] Our aim was to evaluate the surgical work load produced by a screening service run by non-medical staff in terms of the rates of referral for consultation and biopsy.

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ANNEX 22

To: Dr Charlotte Hawkins MHRA/PL

From: Dr Emma Heeley MHRA/PL

Date: 15 April 2004

c.c. Dr Jane Moseley MHRA/PL

RE: USAGE DATA FOR CO-PROXAMOL BY 10 YEAR AGE BANDS

PURPOSE:

Primary Care

DiseaseAnalyzer - Mediplus

This database contains anonymised computerised longitudinal records of patients' GP consultations and treatment. The practices are reported to be representative of the geographical distribution of GPs in the UK and the figures can be projected up to estimate UK numbers. The database contains the records of around 3.5 million patients of which half are currently active. Birth year is recorded rather than date of birth which means that age categories cannot be well defined.

Patients who were issued with a prescription for co-proxamol in the past 12 months of data (1/10/2002 – 30/9/2003) were identified in the Disease Analyzer Mediplus database. The ages of these patients are presented in table 1. These figures were projected up to estimate the age distribution of the patients being issued with prescriptions in primary care in the UK (table 2). The estimated total number of patients prescribed co-proxamol in prmary care in the UK is 1.7 million patients. It is important to note that this does not take into account over the counter use or hospital prescribing. The total number of patients in each age band is not a sum of the use of the two products as a patient may have been prescribed both products in the past 12 months.

Table 1 Age distribution of patients issued with a prescription for co-proxamol in Disease Analyzer Mediplus from 1/10/2002 to 30/9/2003

Patient age(years)	Co Proxamol	Distalgesic	Total
10-19	271		271
20-29	1,091	1	1,092
30-39	2,189		2,189
40-49	2,995		2,995
50-59	4,229	3	4,231
60-69	6,073	3	6,075
70-79	7,050	7	7,054
80-89	4,555	7	4,559
90-99	905		905
100-109	25		25
120-129	1		1
Total	29,384	21	29,397

Table 2 Age distribution of projected number of patients issued with a prescription for co-proxamol in primary care in the UK from 1/10/2002 to 30/9/2003

Patient age(years)	Co Proxamol	Distalgesic	Total
10-19	15,528	0	15,528
20-29	62,514	57	62,572
30-39	125,430	0	125,430
40-49	171,614	0	171,614
50-59	242,322	172	242,436
60-69	347,983	172	348,098
70-79	403,965	401	404,194
80-89	261,002	401	261,231
90-99	51,857	0	51,857
100-109	1,433	0	1,433
120-129	57	0	57
Total	1683703	1203.3	1,684,448

DiseaseAnalyzer Mediplus data is provided by IMS Health and these data must not be released outside the agency without permission from IMS Health.

For further information on all databases please refer to the Pharmacoepidemiology intranet pages http://mcanet/pld_intranet/pharmacovigilance/D[illegible]SourcesEpi.htm

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ANNEX 23

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Suicide in young people

Study of 174 cases, aged under 25 years, based on coroners' and medical records

KEITH HAWTON, KELLY HOUSTON and ROSIE SHEPPERD

Background Suicide rates in young males in the UK have risen markedly in recent years.

Aims To investigate the characteristics of a series of consecutive suicides in under-25-year-olds.

Method We studied coroners' inquest notes, general practitioners' records and psychiatric case notes of 174 individuals (148 males and 26 females) whose deaths received a verdict of suicide or an open or accidental verdict (excluding traffic accidents) where the circumstances strongly suggested suicide.

Results More individuals were of lower social class and unemployed than in the local population. Hanging and carbon monoxide poisoning were the most frequent methods of suicide, and co-proxamol was the drug most often used in overdoses. Previous self-harm had occurred in 44.8%, nearly half of these having carried out multiple episodes and 80% having self-harmed within the previous year. Little support was found for an earlier finding of increasing frequency of general practitioner visits shortly before death. Only 22.4% of individuals were in the care of psychiatric services.

Conclusions Diverse strategies are required to prevent suicide in the very young.

Declaration of interest Support received from the former Oxford Regional Health Authority and the Anglia and Oxford Research and Development Committee.

In the UK in recent years a substantial increase in rates of suicide and possible suicides has occurred in young males (Charlton *et al*, 1992; Hawton, 1992). Although there are early signs of a reversal in this pattern (Kelly & Bunting, 1998), their rates of suicide remain alarmingly high. More knowledge about the nature and causes of suicide in the young is needed to inform prevention policies. Although the most informative means of studying the causes of suicide is through the psychological autopsy approach (Brent *et al*, 1988; Hawton *et al*, 1998*a*), there are some important aspects of the suicidal process that can be investigated using coroners' inquest notes and medical records (Cattell & Jolley, 1995). We have used these sources to investigate a large series of under-25-year-olds who died by suicide and probable suicide, in order to study various socio-demographic and clinical aspects of the suicidal process. We have also investigated whether the crescendo of contacts with general practitioners shortly before suicide reported by Appleby *et al* (1996) in under-35-year-olds also occurs in very young suicides.

METHOD

Subjects

The subjects were individuals under the age of 25 years who died between January 1990 and June 1995, whose deaths were the subject of an inquest by any of the six coroners in the former Oxford Regional Health Authority area (Berkshire, Buckinghamshire, Oxfordshire and Northampronshire), where the verdict or other information in the coroners' records indicated that the death had been from suicide or probable suicide. All deaths where a verdict of suicide was recorded were included. In addition, the coroners' records for all cases that had received a verdict of undetermined cause (open) or accidental death (excluding road traffic accidents) were scrutinised to determine the possibility of suicide. These cases were given a rating of definite, probable (> 50% likelihood) or unlikely suicide. This rating, which was decided at consensus meetings, was based on the examination of the following factors: planning, intent, suicidal communication and lethality of method. Cases that were rated as definite or probable suicides were included in the study.

During the study period, a total of 123 suicide verdicts, 54 open verdicts and 37 accidental verdicts (excluding road traffic accidents) were recorded by the coroners in the 15–24-year age band. Of the open verdicts, the probability of suicide was rated as definite or probable in 38 cases (70.4%); and of the accidental verdicts, the likelihood of suicide was rated as definite or probable in 13 cases (35.1%). Thus, a total of 174 individuals were included in the study.

Sources of information

Information was collected from the following sources.

Coroners' inquest records

These were available for all the cases.

General practitioners' records

These were sought in all cases, including those involving prison medical services and military services where appropriate. Medical records were obtained for 107 cases (65.2%). Of those cases for which medical records were not obtained, in 10 cases the individual was not registered with a general practitioner, in 38 the notes had been destroyed (deaths that occurred in 1990 and 1991), in 17 the notes were lost and in 2 the general practitioner refused access. Thus, medical notes were obtained for 107 out of 109 individuals (98.2%) for whom the medical notes were available.

Psychiatric case notes

The psychiatric records were requested for all individuals who were known to have been in psychiatric care at any time (n=49) and were obtained in 45 (92.0%) cases.

Information collected

The information was extracted onto a standardised structured data form and included the following.

Demographic and social information

Comparisons were made between the social class distribution and employment status of the study population and that of the local general population based on the 1991 Census data. The social class distribution data from the 1991 Census was for all age groups, but it was possible to compare data on employment status for the 16–24-year age group.

Method of suicide and circumstances of the death

Information was collected on the method of suicide and how the subject gained access to the method. We recorded whether a suicide note was left and, if so, the nature of its contents.

General practitioner contacts

The contacts made with general practitioners by individuals during the year before death were studied in detail, including the apparent reasons for the contacts and treatments provided. The number of contacts in each week during the final three months before death were recorded.

Psychiatric history

This included contacts with psychiatric services, treatment received at the time of death and within the last year, previous suicide attempts and evidence of suicidal communication. The use of any psychotropic medication (prescribed from any source) was recorded. For patients on antidepressants, the dose prescribed at the time of death was categorised as: *therapeutic* (equivalent to 150 mg amitriptyline), *low therapeutic* (equivalent to 75 mg amitriptyline) and *inadequate* (less than 75 mg amitriptyline).

The study had the approval of the local psychiatric ethics committee.

Statistical analyses

The statistical analyses were conducted using SPSSX (SPSS, 1993).

RESULTS

The study population

The study included 174 individuals. A suicide verdict was recorded in 123 (70.7%) cases, an open verdict in 38 (21.8%) and an accidental verdict in 13 (7.5%). Of the cases where an open or accidental verdict was recorded ($n=51$), the probability of suicide was rated as definite in 25 cases and probable in 26. Eighty-five per cent of the sample were male (Table 1). The majority of subjects were aged 20–24 years (68.4%). The youngest individual was aged 13 years. Most of the subjects were Caucasian (87.9%). There was a markedly different social class distribution in the subjects compared with the social class distribution of the local population from the 1991 Census data (for all age groups), with 61.6% (90/140) of those where the social class was known being in social classes IIIM–V compared with 39.9% of the general population (odds ratio=2.59, 95% CI=1.81–3.71, $P<0.0001$). Far more of the subjects were unemployed (49.6%, 17/135, of those who were economically active) compared with the unemployment rate based on the 1991 Census data for the same age group in the local population (11.1%; odds ratio=7.89, 95% CI=5.55–11.20, $P<0.0001$). Eighteen per cent were students, comprising: 16 school pupils, 3 college students, 13 undergraduates and 1 post-graduate.

The majority of subjects were single (161, 92.5%), only nine (5.2%) being married and four (2.3%) separated or divorced. At the time of death, 89 subjects (51.1%) were living with their parents, 22 (12.6%) were living in an institution (military barracks, 2; boarding school, 1; staff residence, 1; prison, 3; hostel, 5; university halls of residence, 5; hospital, 5), 21 (12.1%) were living with friends or other relatives, 19 (10.9%) were living with a partner, 19 (10.9%) were living alone and 4 (2.3%) had no fixed abode.

Table 1 Demographic characteristics of the 174 subjects

	n	%
Gender		
Male	148	85.1
Female	26	14.9
Age		
Under 15 years	2	1.1
15–19 years	53	30.5
20–24 years	119	68.4
Ethnicity		
Caucasian	153	87.9
African	8	4.6
Asian	9	5.2
Not known	4	2.3
Social class		
I	6	3.4
II	21	12.1
III (non-manual)	23	13.2
III (manual)	56	32.2
IV	27	15.5
V	7	4.0
Armed forces	6	3.4
Not known	28	16.1
Employment status		
Employed	68	39.1
Unemployed	67	38.5
Student	31	17.8
Disabled	4	2.3
Housewife	1	0.6
Not known	3	1.7

Methods of suicide

Self-injury was the most frequent method used for suicide (92, 52.9%), self-poisoning being involved in 79 (45.4%) cases and both self-poisoning and self-injury in 3 (1.7%) cases (see Table 2). Of the male deaths, 83 (56.1%) involved self-injury, 62 (41.9%) self-poisoning and in 3 cases (2.0%) both methods were used. Of the female deaths, 17 (65.4%) involved self-poisoning and 9 (34.6%) self-injury. No females used both methods.

Hanging was the most common single method of suicide, followed by carbon monoxide poisoning and overdoses (Table 2). Nine of the overdoses involved more than one drug. The most frequent drug used for self-poisoning was co-proxamol, which was used by 13 (37.1%) of the individuals who took overdoses. Of the eleven cases where the source of the co-proxamol prescription was known, in only three was the co-proxamol prescribed for the subject, the drug having been prescribed for someone else in eight cases. Antidepressants were used in nine cases and paracetamol in six.

Of the 149 cases in which toxicological information on post-mortem alcohol level was available, there was evidence of alcohol consumption shortly before the death in 56 (37.6%). The toxicology results indicated an alcohol blood level of below 80 mg/100 ml in 23 cases (15.4%), 80–150 mg/100 ml in 20 cases (13.4%) and >150 mg/100 ml in 13 cases (8.7%). There was post-mortem evidence of drugs of abuse in only 12 out of 154 cases (7.8%).

Previous deliberate self-harm

Previous episodes of deliberate self-harm were known to have occurred in 78 cases

Table 2 *Methods of suicide*

	Males (n=148)		Females (n=26)		Both (n=174)	
	n	%	n	%	n	%
Hanging	52	35.1	6	23.1	58	33.3
Carbon monoxide	44	29.7	3	11.5	47	27.0
Overdose[1]	21	14.2	14	58.3	35	20.1
Co-proxamol	9		4		13	
Antidepressants	5		4		9	
Paracetamol	3		3		6	
Minor tranquillisers	5		1		6	
Insulin	1		2		3	
Other prescribed	3		0		3	
Opiates	2		0		2	
Other substance	2		5		7	
Jumping	21	14.2	2	7.7	23	13.2
In front of train	12		1		13	
In front of vehicle	4		0		4	
From height	4		1		5	
From train	1		0		1	
Gunshot	6	4.1	0	0.0	6	3.4
Drowning	3	2.0	1	3.8	4	2.3
Burning	2	1.4	0	0.0	2	1.1
Other	2	1.4	0	0.0	2	1.1

Both self-injury and self-poisoning were involved in three cases.
1. Multiple drugs were used in nine cases (49 substances were used in total).

Table 3 Visits to general practitioners during each week in the three months prior to death

Time period before death	Males (n=85)		Females (n=17)		Both (n=102)	
	n	No. of visits	n	No. of visits	n	No. of visits
1 week	15	19	3	4	18	23
2 weeks	12	15	2	2	14	17
3 weeks	9	9	4	5	13	14
4 weeks	9	9	3	3	12	12
1–4 weeks	**27**	**52**	**8**	**14**	**35**	**66**
5 weeks	8	12	2	2	10	14
6 weeks	12	15	2	3	14	18
7 weeks	7	7	1	1	8	8
8 weeks	8	10	4	5	12	15
5–8 weeks	**23**	**44**	**6**	**11**	**29**	**55**
9 weeks	9	10	2	2	11	12
10 weeks	9	11	3	3	12	14
11 weeks	5	5	3	3	8	8
12 weeks	5	5	2	2	7	7
9–12 weeks	**16**	**31**	**7**	**10**	**23**	**41**

(44.8%). In 27 cases it could not be determined whether or not there had been a previous episode. Of those subjects with a history of self-harm, 35 (44.9%) were known to have a history of multiple episodes. The medical outcome of the most recent previous episode of deliberate self-harm was unclear in many cases, but it appeared that a substantial proportion had not been seen at a general hospital. Of the 65 cases where the timing of the previous episode was known, this was within the year before death in 52 cases (80.0%), including 29 (44.6%) within a month and 15 (23.1%) within a week.

Suicide notes

Messages were found after the death in 83 cases (47.7%), there being a total of 153 messages in all. The majority of messages were left for relatives (62, 40.5%) and partners (31, 20.3%). In 42 cases (50.6%) the note contained clear reasons for the suicide and in 18 cases (21.7%) the reasons were ambiguous. The contents of the note were not disclosed in four cases. In the remaining 19 cases, the messages did not contain any reasons, clear or otherwise, for the death.

Suicidal communication

Ninety-four subjects (54.0%) were known to have expressed suicidal thoughts within the year before death and 77 (44.3%) within the month before death. Of the latter, 52 made clear statements of intent and 25 spoke more ambiguously. Relatives were most often the recipients of the communications (43, 24.7%), followed by professionals (35, 20.1%), partners (25, 14.4%) and friends (22, 12.6%).

General practitioner contact

Out of the total sample, 164 subjects (94.3%) were known to have been registered with a general practitioner at the time of death. Details regarding contact with the general practitioner in the year before death were available for 102 cases out of the 107 for which medical notes were obtained. The timing of the last visit to the general practitioner was within 24 hours in seven cases (6.8%), within one week in 11 cases (10.8%), within one month in 18 cases (17.6%) and within six months in 30 cases (29.4%). The cumulative number of subjects having contact with their general practitioner was 18 (17.6%) within the week before death, 35 (34.3%) within the month beforehand and 51 (50.0%) within the three months beforehand. In all, 80 subjects (78.4%) had seen their general practitioner within the last year of life.

The timing of consultations in the three months before death was examined in detail (Table 3). We found a similar crescendo

effect to that of Appleby *et al* (1996) in the number of visits during each one-month period in the three months before death, but the increase was not statistically significant for either gender (males: $\chi^2=5.31$, d.f.=2, $P<0.10$; females; $\chi^2=0.74$, d.f.=2, $P<0.7$).

Psychiatric care

At the time of death, 39 subjects (22.4%) were receiving treatment from psychiatric services: 29 as out-patients and 10 as in-patients. Thirty-eight subjects (21.8%) were receiving psychotropic medication, including 25 who were prescribed antidepressants (of whom eight were on a low or inadequate dose), 16 who were prescribed antipsychotics and 7 who were prescribed benzodiazepines.

Fifty-two subjects (29.9%) were known to have had contact with mental health services in the year before death, with 38 seeing more than one mental health professional. Mental health professionals seen included psychiatrists (47), psychologists (11), psychiatric nurses (22), community psychiatric nurses (28) and social workers (22). In addition, 18 individuals had seen a counsellor and 8 had contacted a self-help group. Seventy-seven subjects (44.3%) were known to have received out-patient treatment, 34 (19.5%) had received in-patient treatment at some point in their life and 33 (19.0%) had received both. Of the subjects for whom general practitioner notes were available ($n=107$), 50 subjects (46.7%) had never had any contact with a mental health professional.

DISCUSSION

We have studied a large sample of adolescents and very young adults who died by suicide or probable suicide. The study population is comprehensive in that we included consecutive suicides and also open verdicts and accidental deaths (excluding road traffic accidents) in which there was reasonable evidence that they were in fact suicides. The importance of including open and accidental verdicts in studying suicides is well recognised (Charlton *et al*, 1992) and the particular importance of this strategy in young people has been demonstrated recently by Madge & Harvey (1999). Although general practitioner notes could be obtained only for two-thirds of the sample, only two general practitioners refused access to the medical records. In the majority of cases for which no medical records were obtained, the deaths had occurred in the first two years of the study period and the notes were either destroyed or lost. Thus, there is unlikely to have been any systematic bias in this information, although the power of this aspect of the study was somewhat reduced.

We have deliberately restricted our study to the examination of items that are likely to be reliable using inquest, medical and psychiatric records. In order to investigate other factors such as personal history, interpersonal relationships, problems and details of psychiatric disorder, it is necessary to use the psychological autopsy approach (Brent *et al*, 1988; Hawton *et al*, 1998*a*), which we have done on a subsample of the total cases and will be reporting separately.

Socio-demographic characteristics

The marked gender difference, with 85% of the sample being male, is in keeping with known rates of suicide within this age group (Charlton *et al*, 1992; Kelly & Bunting, 1998). Similarly, the fact that two-thirds were between the ages of 20 and 24 years is in keeping with the increase in rates of suicide between older adolescence and young adulthood (Kelly & Bunting, 1998). The skewed social class distribution compared to local population data, with an excess of subjects being in the lower social class groups, is a new finding, although it is recognised for suicides of all ages (Kreitman *et al*, 1991). An association of suicide with unemployment in adults is well recognised (Platt, 1984). We have demonstrated this in the present population of very young suicides. It is important to recognise, however, that the nature of this association is often unclear and the actual contribution of unemployment in the aetiology of suicide may be less than expected (Beautrais *et al*, 1998).

Methods used for suicide

There has been a recent increase in hanging in young people of both genders in England and Wales (Kelly & Bunting, 1998) and our finding that one-third of the study population died this way, including a quarter of the females, is in keeping with this trend. Prevention by restricting the availability of the means for this method is clearly difficult, except in psychiatric units. The high proportion of the sample who used carbon monoxide (i.e. car exhaust fumes) is also in keeping with national figures (Kelly & Bunting, 1998), but there is preliminary evidence that this method has started to become less frequent as the number of cars fitted with catalytic converters has increased (Wilson *et al*, 1998). It will, however, take some time before there is a substantial effect in the very young because they are less likely to have access to new cars.

The risk of death from paracetamol self-poisoning is well recognised. However, the fact that the most frequent method of overdose was with co-proxamol (i.e. paracetamol and dextropropoxyphene) needs to be highlighted. This is a very dangerous drug in overdose with death usually ensuing rapidly due to the respiratory depressant effect of dextropropoxyphene (Lawson & Northridge, 1987). It is, however, a prescription-only drug and, therefore, it is of particular concern that in most cases the drug had been prescribed for someone other than the person who died. We do not know whether it was chosen simply because it was available in the home or because the individual knew of its dangers. The extent to which it is prescribed and the doses available should be examined to see whether its availability can be limited further.

Alcohol clearly made a contribution to the suicidal acts of a sizeable proportion of the individuals, excessive blood alcohol levels being found at post-mortem in over one-fifth of cases. It is notable that very few individuals had post-mortem evidence of having used drugs of abuse shortly before their death.

Previous deliberate self-harm

The proportion of individuals who had engaged in previous acts of deliberate self-harm (44.8%) is far higher than in studies from other countries (Brent *et al*, 1993; Martunnen *et al*, 1993; Shaffer *et al*, 1996) and yet is likely to be an underestimate because of minimal information in a sizeable proportion of cases. This may reflect the relatively high rates of non-fatal self-harm in young people in the UK (Schmidtke *et al*, 1996) and the greater chance of dying at the first attempt in countries such as the USA and Finland where there is ready access to guns. The risk of suicide following deliberate self-harm in young people is well documented (Otto, 1972; Goldacre & Hawton, 1985; Sellar *et al*, 1990; Hawton *et al*, 1993). Nevertheless,

our findings underline the importance of ensuring that adequate services for this population are available in general hospitals (Royal College of Psychiatrists, 1994, 1998). The fact that a substantial proportion of those who had engaged in previous self-harm had neither been referred to the general hospital nor seen their general practitioner suggests that the significance of the self-harm, as well as the expression of suicidal ideation, which was also frequent, needs emphasising in public education so that more individuals at risk can receive attention from clinical and other support agencies. Although evidence for the efficacy of treatment following deliberate self-harm is currently not strong, mainly because trials have been underpowered (Hawton *et al*, 1998*b*), the fact that a non-fatal suicidal act is the most important predictor of possible future suicide means that this significant marker of risk must not be neglected.

Contact with clinical services and opportunities for prevention

General practitioner attention to individuals at risk is often emphasised as a potential prevention strategy, and indeed half of our sample had seen a general practitioner within three months of death and one-third within a month. These figures would be reduced a little if the ten subjects not registered with a general practitioner were included in the calculation. The difficulty of detecting those at risk from the many more young people who present with psychosocial difficulties and mental health problems is a very real one. We found a trend similar to that of Appleby *et al* (1996), who reported an increase in general practice attendance by under-35-year-olds in the three months before death, but the increase was not statistically significant and, therefore, unlikely to be a useful indicator of risk.

Although nearly one-third of the sample (29.9%) had been in psychiatric care in the year before death (details of this will be reported separately), it is important to emphasise that nearly half had never been in psychiatric care. This underlines the fact that prevention of suicide in the young extends way beyond psychiatric services and that an effective prevention programme demands attention to many factors, including economic and education strategies, further restriction in the availability of dangerous means and modification of media reporting and portrayal of suicide. Also, the public needs to be made more aware of the significance of the communication of suicidal thoughts by young people.

CLINICAL IMPLICATIONS

- The finding that nearly half of a large series of young suicides had carried out an act of deliberate self-harm in the year before death emphasises the need to ensure that clinical services for young people who harm themselves are of a high quality.
- Suicidal ideas are frequently expressed before suicide in young people and should be taken seriously.
- The use of co-proxamol in several suicides raises concerns about its availability in spite of it being a prescription-only drug.

LIMITATIONS

- Reliance solely on inquest records, general practitioner and psychiatric case notes limited the extent of information that could be examined.
- Lack of a comparison group for most of the findings limits the extent to which they can be used as specific risk factors.
- Verification of the findings through enquiry of informants was not possible on such a large sample.

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ANNEX 24

EXTRACT PERIOD: 01/01/95-03/10/03 EARLIEST REACTION DATE: 31/01/95 REACTION: SERIOUS TYPE:SPONTANEOUS ORIGIN: UK

DRUG : DEXTROPROPOXYPHENE
ROUTE: ALL
SINGLE-CONSTITUENT PRODS : *DOLOXENE*

MULTI-CONSTITUENT PRODS : CO-PROXAMOL (PARACETAMOL)
DISTALGESIC (PARACETAMOL)

SUBSTANCE/VARIANT/NPCG: SUBS

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Cardiovascular disorders				
Sudden death unexplained	0	0	2	2
Cardiac failure (all forms)				
Pulmonary oedema	0	0	1	0
Cardiovascular disease symptoms & signs				
Cyanosis NOS	0	0	1	0
Heart block (all forms)				
Sinoatrial block	0	0	1	0
Hypotension (all forms)				
Hypotension	1	0	3	0
Syncope	0	0	2	0
Cardiac arrhythmias (general)				
Bradycardia NOS (exc foetal)	1	0	2	0
Cardiac arrest	0	0	1	0
Tachycardia NOS	0	0	1	0
ECG abnormal				
QT prolonged	0	0	1	0
SYS ORGAN CLASS TOTAL:	2	0	15	2
Cerebrovascular disorders				
Brain ischaemia (aetiology unspecified)				
Brain stem infarction	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	1	0
Congenital anomalies				
Congenital CNS disorders				
Congenital brain damage	0	0	1	0
Congenital eye disorders				
Anophthalmos	0	0	1	0
Congenital limb deformities				
Congenital hand agenesis	0	0	1	0
Other congenital musculoskeletal deformities				
Achondroplasia	0	0	1	1
Congenital arthrogryposis	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	5	1
Disorders of metabolism & nutrition				
Disorders related to diabetes				
Diabetic control impaired	0	0	1	0
Electrolyte & fluid balance disorders				
Hypokalaemia	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	2	0
Gastrointestinal disorders				
Gastrointestinal disorders NOS				
Peritonitis	0	0	1	0
Gastrointestinal system symptoms & signs				
Haematemesis	0	0	1	0
Melaena	0	0	1	0
Pancreatic disorders				
Pancreatitis acute	0	0	1	0
Upper gastrointestinal ulceration & perforation				
Duodenal ulcer haemorrhage	0	0	1	0
Gastric ulcer	0	0	1	0
Gastric ulcer haemorrhage	0	0	1	0
Gastric ulcer perforated	0	0	1	1
SYS ORGAN CLASS TOTAL:	0	0	8	1
General disorders				
Multiple organ failure	0	0	1	1
General symptoms & signs				
Collapse	0	0	2	0
Therapeutic & non-therapeutic drug responses				
Alcohol interaction	0	0	2	0
Drug interaction NOS	1	0	6	0
Drug interaction potentiation	0	0	1	0
Drug withdrawal reaction	0	0	1	0
SYS ORGAN CLASS TOTAL:	1	0	13	1
Haemopoietic disorders				
Haemorrhage NOS	0	0	2	0
Clotting & coagulation defects (exc platelets)				
International normalised ratio increased	0	0	5	0
Stem cell disorders (exc myeloproliferative disorders)				
Pancytopenia	0	0	1	0
Disorders with decreased white blood cells				
Leucopenia NOS	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	9	0

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL
Hepato-biliary disorders				
Bile duct disorders				
Biliary colic	0	0	1	0
Gall bladder disorders				
Cholecystitis	0	0	1	0
Cholelithiasis	0	0	1	0
Hepatic function abnormalities				
Cholestasis	0	0	1	0
Hepatic function abnormal NOS	1	0	7	0
Hepatitis (all forms)				
Hepatitis NOS	0	0	2	0
Hepatitis cholestatic	0	0	1	0
Hepatocellular damage				
Hepatic failure	0	0	2	0
Hepatocellular damage NOS	0	0	2	0
Jaundice (all forms)				
Jaundice NOS	0	0	5	0
Jaundice cholestatic	0	0	3	0
SYS ORGAN CLASS TOTAL:	1	0	26	0
Injury & poisoning				
Overdose & poisoning				
Non-accidental overdose	1	1	8	1
Overdose NOS	0	0	10	4
SYS ORGAN CLASS TOTAL:	1	1	18	5
Musculoskeletal, connective tissue & bone disorders				
Arthropathies nonspecific				
Arthralgia	0	0	1	0
Arthritis	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	2	0
Neurological disorders				
Convulsions & epilepsy				
Convulsions NOS	1	0	3	0
Epilepsy aggravated	0	0	1	0
Grand mal convulsion	0	0	1	0
Extrapyramidal disorders (all forms)				
Acute dystonic reaction	0	0	2	0
Dystonia	0	0	1	0
Oculogyric crisis	0	0	1	0
SYS ORGAN CLASS TOTAL:	1	0	9	0
Pregnancy, puerperium & perinatal conditions				
Abortion & stillbirth				
Spontaneous abortion	1	0	0	0
SYS ORGAN CLASS TOTAL:	1	0	0	0
Psychiatric disorders				
Psychiatric symptoms & signs				
Aggression	0	0	1	0
Confusion	0	0	2	0
Hallucinations	0	0	3	0
Suicide & parasuicide				
Suicide (accomplished)	0	0	3	3
Drug dependence (all forms)				
Drug dependence NOS	1	0	6	0
Drug misuse (non dependent)				
Drug abuse NOS	1	0	0	0
SYS ORGAN CLASS TOTAL:	2	0	15	3
Renal & urinary disorders				
Urinary disease symptoms & signs				
Urinary incontinence	0	0	1	0
Renal failure (all forms)				
Renal failure NOS	0	0	1	1
Renal impairment NOS	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	3	1
Respiratory disorders				
Ventilatory disorders (exc foetal & neonatal)				
Apnoeic attack	1	0	1	0
Asphyxia	0	0	1	1
Respiratory depression	0	0	1	1
Respiratory failure (exc neonatal)	0	0	2	2
Obstructive airways disorders				
Bronchospasm	0	0	1	0
Parenchymal lung disorders				
Hypersensitivity pneumonitis	0	0	1	0
SYS ORGAN CLASS TOTAL:	1	0	7	4
Skin & subcutaneous tissue disorders				
Bullous dermatoses				
Pemphigoid	0	0	1	0
Vascular abnormalities of skin				
Ecchymoses	0	0	3	0
Angioedema				
Face oedema	0	0	1	0
Periorbital oedema	0	0	1	0
SYS ORGAN CLASS TOTAL:	0	0	6	0
TOTAL REACTIONS FOR DRUG:	10	1	139	18

TOTAL REPORTS: 96 TOTAL FATAL OUTCOME: 19

SYSTEM ORGAN CLASS / HIGH LEVEL TERM / REACTION NAME	SINGLE CONST TOT	SINGLE CONST FTL	MULTI CONST TOT	MULTI CONST FTL

*** END OF REPORT ***

ANNEX 25

Letters

Co-proxamol and suicide

Licence needs to be changed

EDITOR—We agree with Hawton et al that co-proxamol presents a major overdose hazard, their results illustrating the difficulties for licensing authorities in limiting availability of prescription medicines that are only hazardous in overdose.[1]

Co-proxamol is more likely to result in death; it causes prolongation of the QRS interval in an electrocardiogram in experimental animals and in humans.[2,3] This property is usually associated with sodium channel blockade and is a precursor to ventricular arrhythmia. We have shown a significant relation between estimated dextropropoxyphene dose (based on paracetamol concentration) and QRS prolongation in a case of co-proxamol poisoning,[4] an effect not seen with other opioid combination products.

Dextropropoxyphene is rapidly absorbed from the gastrointestinal tract, increasing early cardiac risk, with death happening within one hour after ingestion.[5] Most patients probably die of co-proxamol poisoning as a result of its combined cardiac (non-opioid) and central nervous system (opioid) effects before hospital admission. Understanding these factors may also improve acute care.

Prescribing patterns for co-proxamol may show geographical variation, which could alter the risk estimates calculated by Hawton et al. In Edinburgh co-proxamol poisoning accounted for 4.8% of 5583 patients admitted with self harm in the two years from July 2000 to June 2002 (overall 20% of patients took an opioid). These figures seem similar to those of Hawton et al.

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Competing interests: None declared.

1 Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. *BMJ* 2003;326:1006-8. (10 May.)
2 Nickander RC, Emmerson JL, Hynes MD, Steinberg MI, Sullivan HR. Pharmacologic and toxic effects in animals of dextropropoxyphene and its major metabolite norpropoxyphene: a review. *Hum Toxicol* 1984;3(suppl):S13-36.
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4 Afshari R, Bateman DN. ECG abnormalities in co-proxamol (paracetamol/dextropropoxyphene) poisoning. *J Toxicol Clin Toxicol* (in press).
5 Whittington RM. Dextropropoxyphene deaths: coroner's report. *Hum Toxicol* 1984;3(suppl):S175-85.

Co-proxamol should be restricted, not banned

EDITOR—Smith suggests that co-proxamol be banned.[1] I am surprised by this reaction to Hawton et al's paper on co-proxamol and suicide.[2] Hawton et al clearly advocate restricting the availability of co-proxamol.

Dextropropoxyphene is closely related to methadone, and like methadone it has noradrenergic analgesic properties in addition to its opioid effect. Patients who attend pain clinics have often tried several compound analgesics, and occasionally they report that co-proxamol is the most effective. This may reflect a neuropathic component to their pain that is quite different to the postoperative pain for which co-proxamol is no better than paracetamol alone.

The evidence suggests that co-proxamol should be restricted perhaps to specialist use but not banned outright. After all a knee jerk ban of thalidomide would have deprived medicine of a drug still used in the treatment of leprosy.

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Competing interests: None declared.

1 Smith R. Choice: Unknown unknowns in suicide and depression. *BMJ* 2003;326 (7397):0. (10 May.)
2 Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. *BMJ* 2003;326:1006-8. (10 May.)

Availability of co-proxamol has been successfully reduced in Doncaster

EDITOR—In 1998 an audit of suicides in Doncaster identified the alarming rate of co-proxamol overdose as a method of suicide: of the 44 suicides with prescribed drugs between 1995 and 1998, 18 were with co-proxamol (41%).[1] That this is much higher than the national figure of 18% quoted by Hawton et al[2] may be because the rates of prescribing of co-proxamol in Doncaster (around 11 million tablets a year) were 65% higher than the national average.

Hawton et al recommend restricting co-proxamol on the evidence that restricting availability of a specific means of suicide can reduce deaths. Doncaster Health Authority reached the same conclusion in 1998 and undertook to reduce the amount of co-proxamol in circulation by asking general practitioners to be more cautious in prescribing the drug. Doncaster Royal Infirmary also removed co-proxamol from its formulary.

The table shows how, four years on, the policy of reducing prescribing has been successfully implemented: around 60% fewer tablets are currently prescribed than in the period up to 1998 and the prescribing rate is now lower than the national average.

The numbers of suicides among Doncaster residents, also shown in the table, are too small for us to show any relation between the amount of co-proxamol prescribed and the number of suicides with the drug or the total number of suicides. However, we cannot help but be encouraged by the numbers: only five since the beginning of 2000.

The remarkably low number of suicides in 2002 is not a final figure, but many more are unlikely to emerge, and this clearly cannot be attributed to reductions in co-proxamol prescribing. We can, however, be sure that the quantity of tablets in circulation has been massively reduced and that the evidence, as quoted by Hawton et al, implies that this is likely to reduce deaths.

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Competing interests: None declared.

1 Sims A. *Doncaster suicide audit.* Doncaster: Doncaster Health Authority, 1998.
2 Hawton K, Simkin S, Deeks J. Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. *BMJ* 2003;326:1006-8. (10 May.)

Effectiveness of reducing prescriptions of co-proxamol in Doncaster

	1996	1997	1998	1999	2000	2001	2002
No of co-proxamol tablets per prescribing unit*:							
Doncaster	27.9	28.0	26.7	17.6	13.1	11.7	10.7
England and Wales	16.9	16.7	16.4	15.9	15.1	14.5	13.8
No of suicides†:							
With co-proxamol	5	3	7	5	2	3	0
All other methods	25	29	36	22	31	26	14

*Based on data from the Prescription Pricing Authority for preceding eight months for 1996 and on first six months only for 2002.
†Office for National Statistics public health mortality file; data for 2002 not final.

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ANNEX 26

Annex 30: MPA warnings on overdose and ingestion of alcohol in SPCs, PILs and labelling
(Informal translation)

ADDITIONS TO:

Summary of product characteristics:

4.3 Contraindication
Misuse or concomitant use of alcohol and CNS-depressing psychotropic drugs (se 4.4).

4.4 Special warnings and precautions for use
Alcohol should never be used concomitantly with "name of DXP product".

Even at normal doses DXP taken together with alcohol or an overdose of DXP alone, can quickly lead to life threatening respiratory paralysis and cardiac effects. To avoid interaction with alcohol, 1 day must pass after intake of alcohol before treatment with DXP is initiated. The elimination half-life for DXP exhibits great inter individual variation. Therefore it is difficult to give an exact time interval for when alcohol can be consumed after treatment has stopped without risk of interaction. At least two days should pass between ended DXP treatment and alcohol consumption. Se section 5.2 Pharmacokinetics, 4.3 Contraindications, 4.5 Interactions, 4.9 Overdose.

Concomitant use of DXP and medicinal products with a CNS-depressing effect such as barbiturates, benzodiazepines, antidepressants, antiepileptics, morphine analgesics and neuroleptics should be avoided since the risk of respiratory paralysis increases (se also section 4.3 Contraindications and 4.5 Interactions). DXP containing medicinal products should be prescribed with restriction and preferably in smaller packages. The patient should be informed of the importance of following the prescribed dose and of the risks with concomitant use of alcohol.

"Name of DXP product" should not be prescribed to patients that abuse alcohol or where abuse of products with CNS depressing effect can be suspected.
Misuse of DXP has been described. See also under 4.5 interactions."

Package leaflet:

When not to use "name of DXP product"
Intake of "name of DXP product" with alcohol as well as overdose of "name of DXP product" can quickly lead to life threatening respiratory paralysis and cardiac effects. Never drink alcohol concomitantly with "name of DXP product".

If you have drunk alcohol 1 day must pass before you can start treatment with "name of DXP product". The active substance DXP is digested and eliminated at different rates in different individuals. At least 2 days must have passed after ending treatment with "name of DXP product" before you can drink alcohol.

What to avoid when using "name of DXP product"
Avoid alcohol when using "name of DXP product".

Dosing
The recommended dose must never be exceeded
(Used to say "not" instead of "never")

Overdose
Overdose can lead to life threatening respiratory paralysis and serious cardiac effects. If you take too much of the medicinal product contact a doctor, the hospital or the Swedish Poisons Information Centre for evaluation of risk and for advice

Storing
Keep out of the reach and sight of children and adolescents.

Label:

Intake of "name of DXP product" with alcohol as well as overdose of "name of DXP product" can quickly lead to life threatening respiratory paralysis and cardiac effects. Alcohol should never be used with "name of DXP product". Never drink alcohol within 1 day before or 2 days after using "name of DXP product".

ANNEX 27

PATIENT SAFETY

Benzodiazepines warning

Doctors are being reminded that benzodiazepines should only be prescribed for short-term treatment, in light of continued reports about problems with long-term use.

Clear guidance for appropriate use was published in 1988 by the Committee on Safety in Medicines (CSM), which recommended Benzodiazepine should be prescribed for:

- just two to four weeks for relief of severe or disabling anxiety that is subjecting the patient to unacceptable distress; and
- severe or disabling insomnia in patients who are extremely distressed.

They should not be prescribed for the treatment of mild anxiety, according to the CSM.

Although prescribing of benzodiazepines has declined substantially since the release of CSM advice in 1988, prescribing has continued for patients with insomnia and anxiety and for substance mis-users.

Department of Health data show that in 2002, 30% of prescriptions for benzodiazepines were for 56 or more tablets (see box), which suggests a high number of patients are receiving long-term treatment. Long-term use exposes patients to risks such as road traffic accidents, dependence and, in the older population, debilitating falls.

Reducing use

Echoing the CSM advice, the Mental Health National Service Framework (NSF), which was published in 1999, recommended that benzodiazepines should be used for no more than two to four weeks for severe and disabling anxiety.

The Mental Health NSF called upon health authorities to implement systems for monitoring and reviewing prescribing of benzodiazepines within local clinical audit programmes. Primary Care Trusts (PCTs) should ensure that this recommendation is still being implemented.

Experts say consistency in approach and effective communication between primary and secondary care health professionals could help reduce over-prescribing. Such communication could involve the use of shared treatment guidelines that specify duration of therapy and cessation of treatment following hospital discharge.

More attention should be paid to prescribing of benzodiazepines to older people. This could possibly be achieved during the regular medication reviews entitled to all people over 65, according to the Older People's National Service Framework.

Use of benzodiazepines in substance mis-users is still an area of concern. It is estimated that 14% of substance mis-users attending drug treatment centres report benzodiazepine use subsidiary to their main drug use.

Benzodiazepines by the numbers

- General Practitioners in England wrote 12.7 million prescriptions at a cost of £20.9 million in 2002, compared to 15.8 million prescriptions worth £13.8 million in 1992. (Newer agents are more expensive, leading to higher costs despite a drop in prescription volume.)
- 30% of prescriptions were for 56 or more tablets.
- People over 65 years received 56% of prescriptions for the three most commonly prescribed benzodiazepines.

Source: Department of Health, 2002 data, England

The Department of Health is planning to introduce instalment dispensing of benzodiazepines to minimise access to excessive doses for addicted patients. Also, in some parts of the country, specialist clinics are available to help people with benzodiazepine dependence.

For more information on appropriate prescribing, see:

- British National Formulary, guidance on management of benzodiazepine dependence, http://www.bnf.org/.
- Department of Health, Drug Misuse and Dependence, Guidelines on Clinical Management 1999, http://www.doh.gov.uk/drugdep.htm.
- MeReC Briefing, Issue No.17, April 2002, update on benzodiazepines and non-benzodiazepine hypnotics.
- Prodigy, hypnotic and anxiolytic dependence and insomnia, www.prodigy.nhs.uk.
- The Clinical Governance Research and Development Unit at the University of Leicester, audit protocol and data collection forms for prescribing in primary care, www.le.ac.uk/cgrdu/protocol.html.

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Co-proxamol (Distalgesic) Risk:Benefit Evaluation

SCOP & CSM April 2004

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Co-proxamol (Distalgesic)

- Co-proxamol (DXP-P)
  - Dextropropoxyphene (DXP) 32.5mg
  - & Paracetamol (PAR) low dose 325mg
  - Fixed combination for *mild to moderate pain*
  - Marketed 40 years widely used >1.7 million/year
  - 2 tablets, 3 to 4 times a day
- Longstanding concerns about toxicity in overdose
  - CSM action in 1985
  - Re-assessment timely

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Evidence of Benefit: Data

- Li Wan Po 1997 systematic review randomised DB trials single dose
  - Post-op, musculoskeletal, arthritis, moderate pain
  - **PAR 650mg vs DXP-P 65/650**
  - Head to head trials N=202,
  - PAR **650mg**, DXP-P vs Placebo N=1144, 397
- Collins et al 1998 systematic review randomised DB published trials single dose
  - Post-op moderate-severe pain
  - **DXP 65mg, 130mg vs Placebo** N=440, 50
  - **DXP-P vs Placebo** N=963

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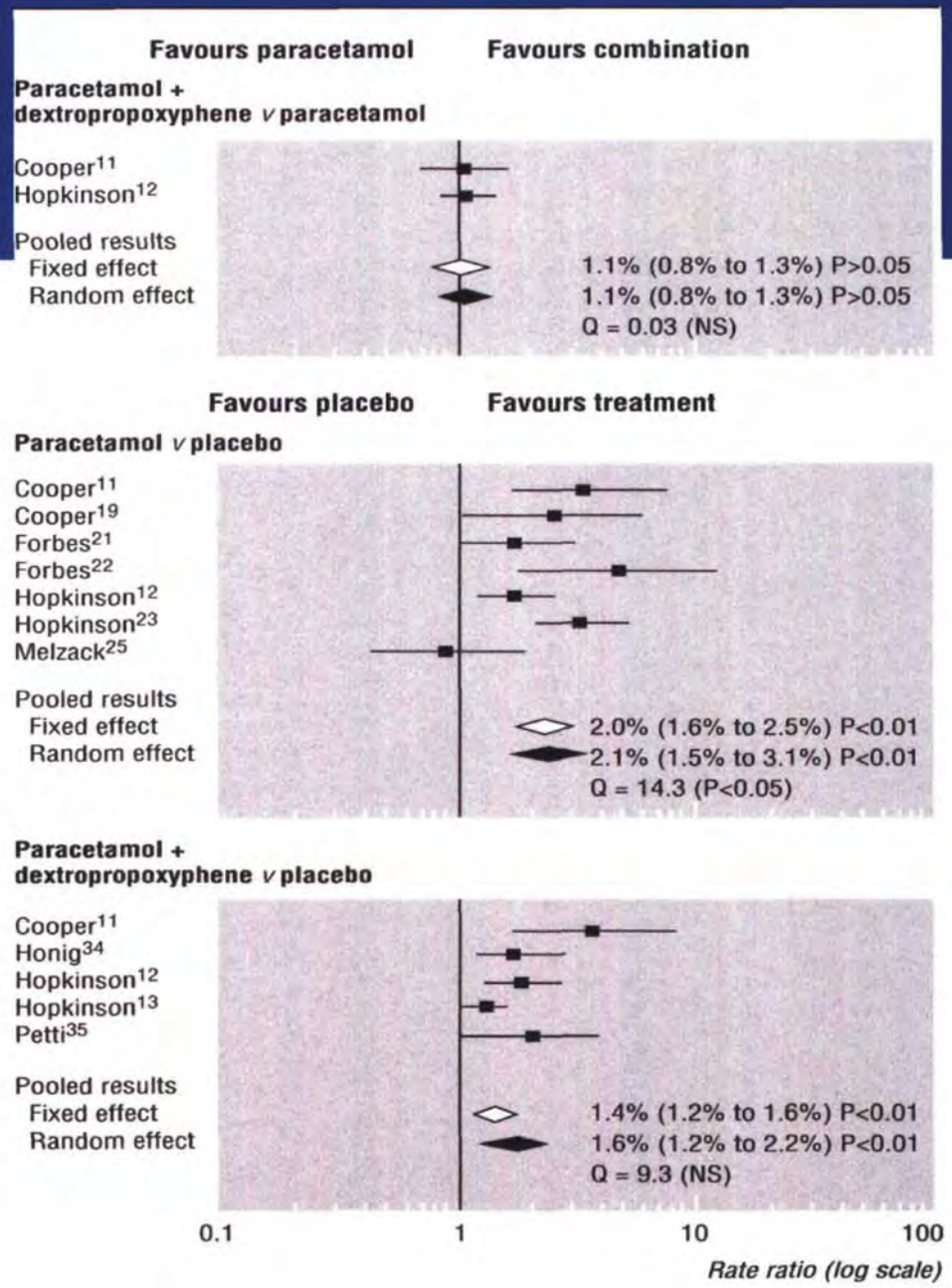

Mean (95% confidence interval) response rate ratios for moderate to excellent pain relief between treatments

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Summary of Benefit: Acute Pain

- Placebo comparisons NNT (Li Wan Po)
  - PAR 650mg vs Placebo: 4 (2.6-5.8)
  - DXP-P 65/650 vs Placebo: 4 (3.1-6.3)

  No additional benefit DXP over PAR 650mg

- Placebo comparisons NNT (Collins)
  - DXP 65mg vs Placebo: 7.7 (4.6-22)
  - DXP 130mg vs Placebo: 2.8 (1.8-6.5)
  - DXP-P vs Placebo: 4.4 (3.5-5.6)

  DXP 65mg alone is not v effective single dose post-op

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Evidence of Benefit: Chronic Pain

- Messick 1979
  - 48 hour RDB Xover study musculoskeletal pain
  - No obvious differences in analgesic efficacy between PAR 650, DXP, DXP-P, N=32
- Owen Hills 1980
  - Cross over study DXP-P/ PAR 1000mg 2 weeks
  - Study details/reasons for patient preference for DXP-P: unknown
- Brooke 1966
  - RDB Xover 3 wks Rh/Deg "Darvon compound significantly rated more effective" in Rh
- Effect of DXP plasma accumulation on efficacy on repeat dosing unknown

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Evidence of UK Risk: 1965-80

- Coroners records/ laboratory analyses DXP-P deaths
  - 30% of drug overdoses, 91% non-hosp deaths
  - Average 15 tablets, min 6 or 8
  - Alcohol associated with 54% of deaths
  - DXP blood levels lower with alcohol 4.8 v 7.2 mg/l
  - 2.0 associated with death (norm 0.05 to 0.75 mg/l)
- Series of fatal / non fatal DXP-P poisonings
  - Fatality rate 12%, esp >20 tabs, depressants
- 300-400 deaths/yr England &Wales mention DXP

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Evidence of UK Risk: 1990-99

- 1997-99 England & Wales **suicide or open verdict**
  - TCAD 22%, DXP-P 18%, PAR 9% of fatal self poisoning
  - DXP-P 255 deaths/yr
  - Odds ratio lethality fatal/ non- fatal self-poisonings
    - DXP-P vs TCAD 2.3
    - DXP-P vs PAR 28.1

- 1990-95 **suicide & definite/probable suicide** (open or accidental verdict) <25 yr age
  - DXP-P commonest agent: 72% others' DXP-P

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Evidence of UK Risk: Suicides 2000-01

- 123 DXP-P poisonings **definite/probable suicides**
- 52% females
- 49% contact with psych services
  - Affective disorder 63%, alcohol dependence 13%
  - Previous self harm history 46%
- 58% with alcohol, more often in younger, less tablets
- Number of tablets min 10, max>100
- Others' DXP-P: 45% in 10-34 yr olds

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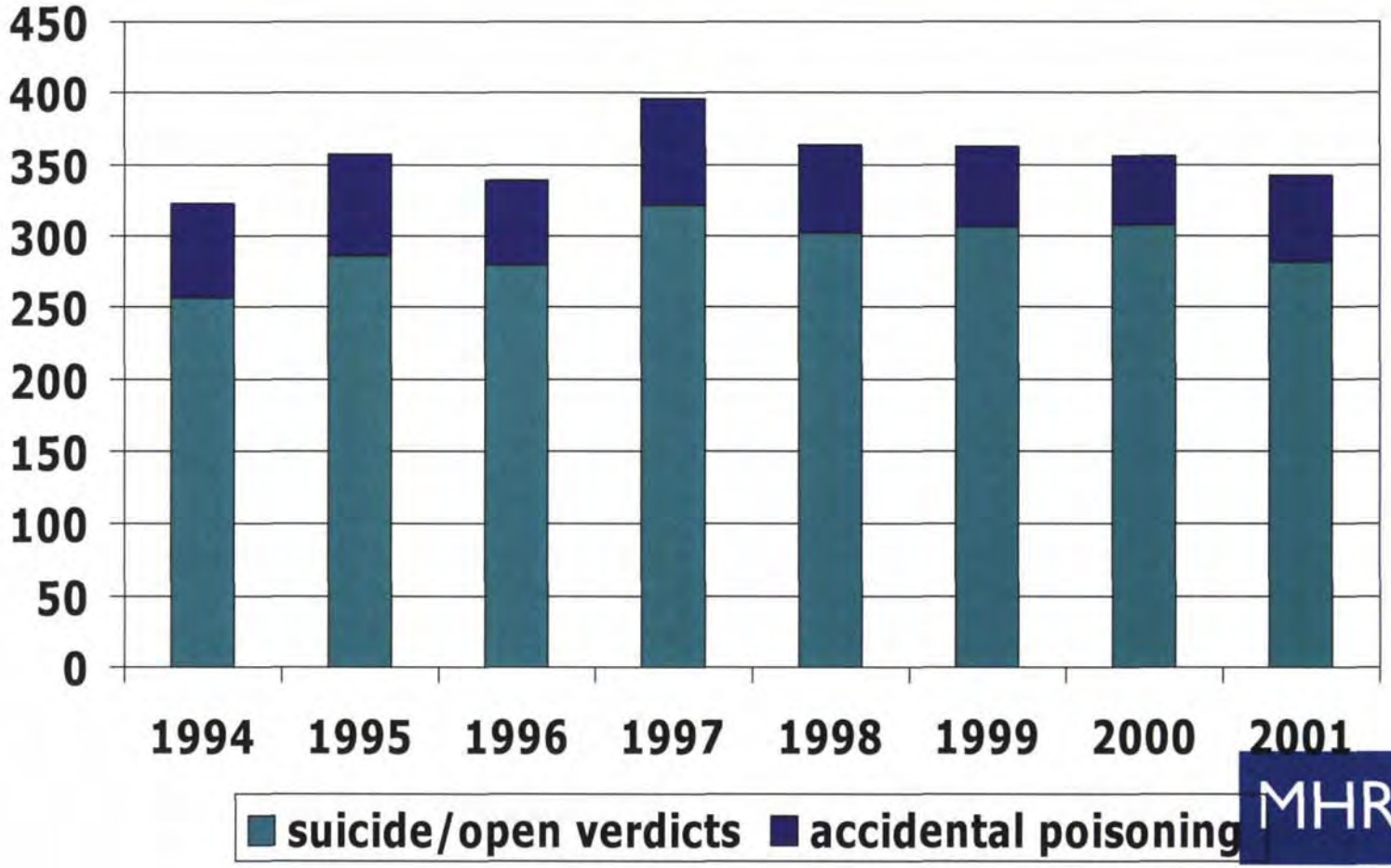
Deaths Mentioning DXP-P E & W



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Other Evidence of Risk

Sweden medico-legal autopsies 1992-6

- Of non suicides, alcohol in 42% (425)
- 12% accidental: non suicides with alcohol, fatal poisoning with DXP

Sweden 1999, analysis of proportionality of prescribing per preparation and breakdown with fatal poisoning

- DXP 26% market but 62% fatal DXP poisoning
- Mean blood DXP higher with single agent than combination

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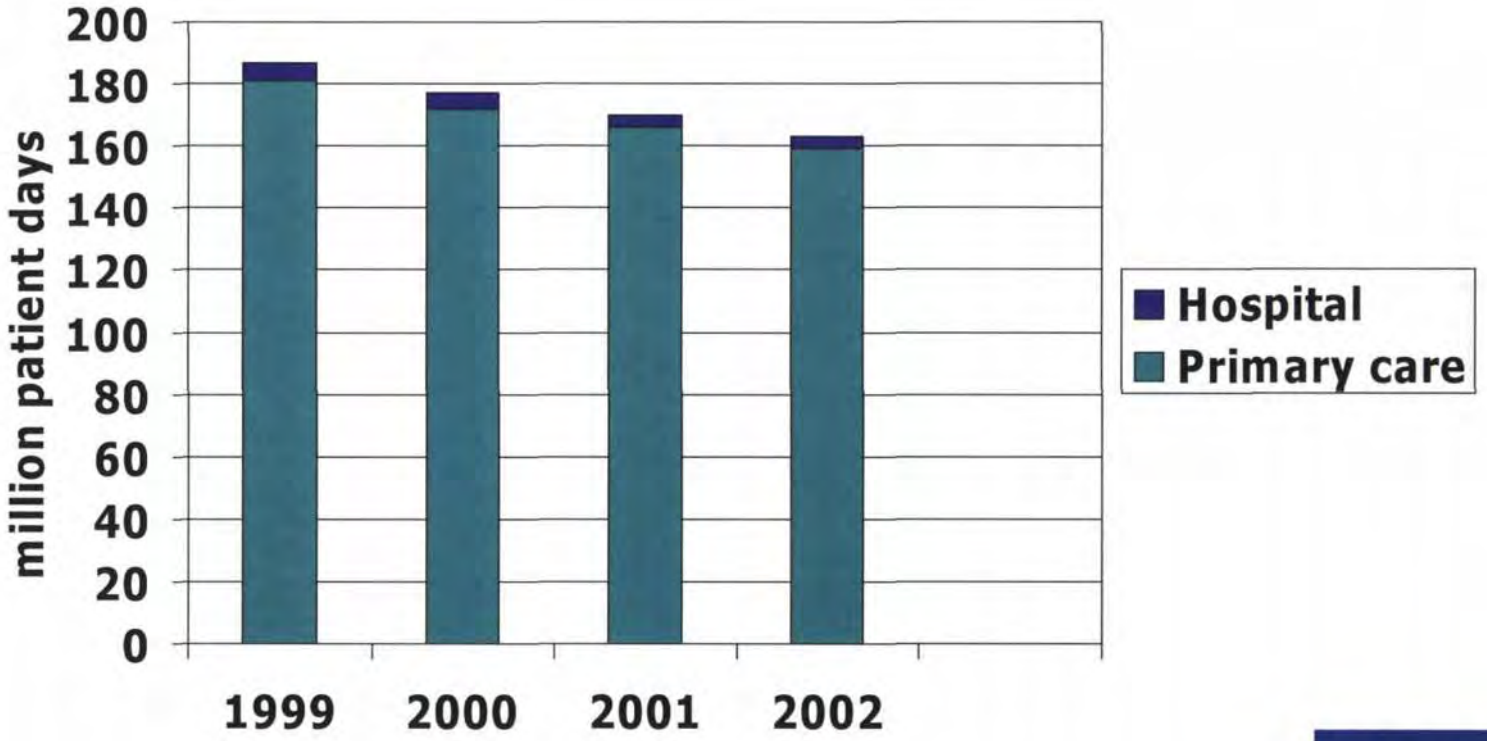
UK Use of DXP-P 1999-2002



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Measures Taken to Reduce Risk

- **Nottingham** nurse and doctor education
  No longer prescribed routinely on wards
- **Doncaster** GP communication &hospital formulary
  60% fewer tables prescribed, fewer suicides?
- **Sweden** Agency communications, product warnings
  Narcotics prescription form 1999-2000, Declining sales & fatal overdoses
- **Australia** 1980 1 hospital DXP-P consultants Rx only
  In patient DXP-P Rx down 98%, OPD 76%
  Increases in simple & compound analgesics

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WHO Pain Ladder

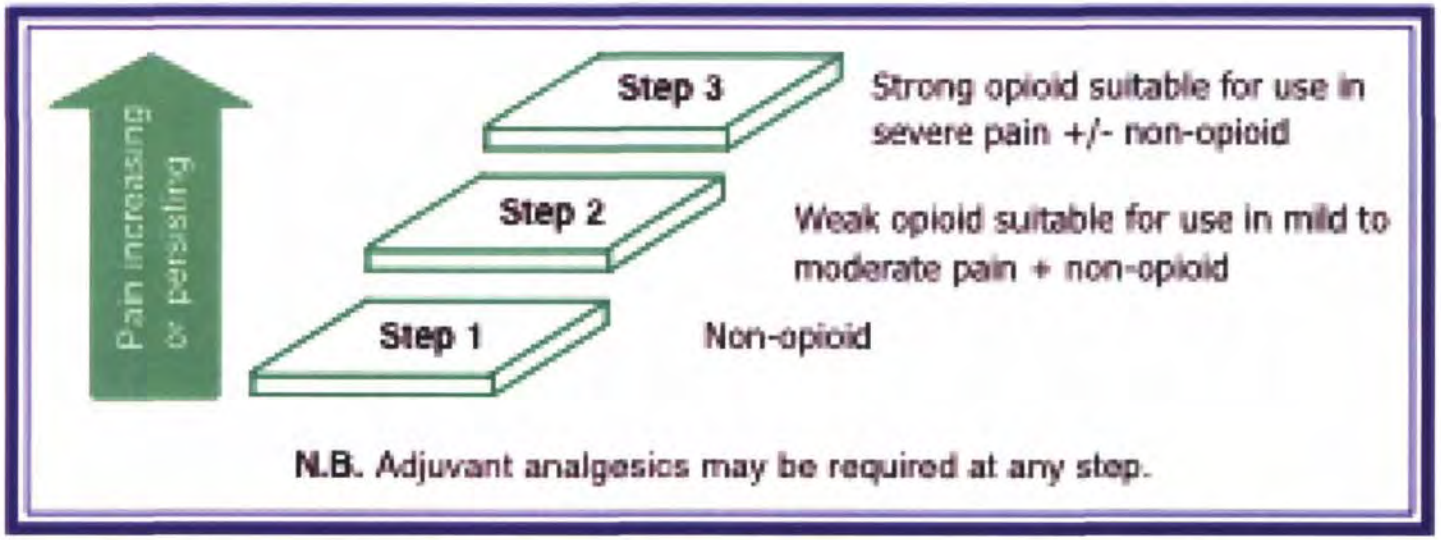

Figure 1. The World Health Organisation (WHO) three-step analgesic ladder[4]

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DXP-P Risk:benefit

- Evidence of benefit
  - Acute pain: no additional benefit to PAR 650mg
  - Chronic pain: robust efficacy evidence lacking and accumulation effects unclear
- Evidence of Risk
  - Toxic dose x1.25 max daily dose, additive effects respiratory depression with CNS depressants,
  - Lethality ratio > than paracetamol or TCADs in overdose
  - 18% drug related suicides, 5% suicides
  - Some fatalities accidental, some possibly impulsive
  - Little opportunity for rescue with rapidity of toxicity
  - Ratio of no. deaths/no. patients prescribed: 1/7,000
  - Continued 300-400 deaths per year E&W mention DXP-P

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Advice Sought

The Committee is asked

- To consider the **risk:benefit** for co-proxamol (Distalgesic) in acute & chronic pain
- To advise which measures should be adopted to reduce toxicity in overdose

1. **Revocation** of the marketing authorisations for co-proxamol (Distalgesic)
2. **Restriction** of indications to:

   chronic osteoarthritis, neuropathic pain and cancer pain
3. Strengthening of **product information**, especially labels & leaflets
4. Encouraging the availability of a wider range of **(smaller) packs**
5. An **education & communication** strategy to change prescribing practice

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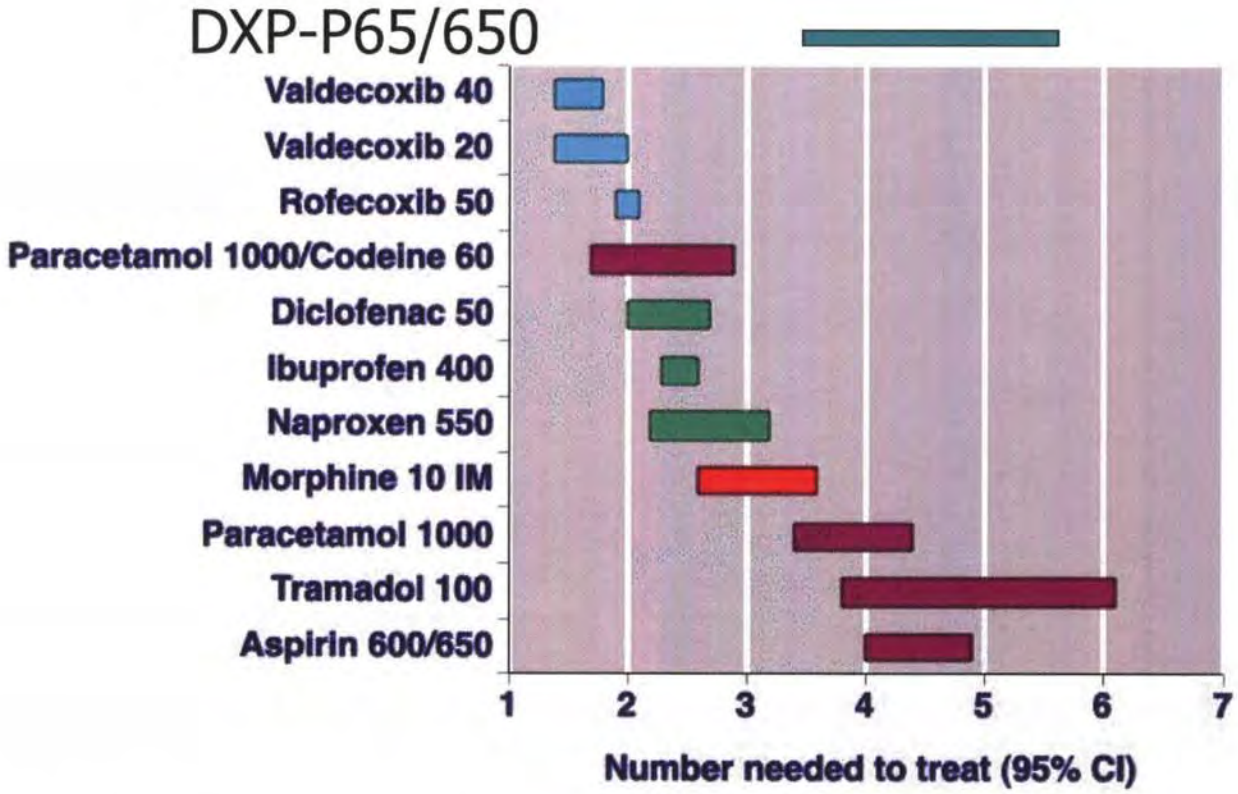
Relative Efficacy Vs Placebo



Moderate severe pain single oral dose at least 50% pain relief over 4-6 hours

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