Between 1983 and 1993 the number of outpatient visits in the USA increased by 75%, while the number of inpatient days fell by 21%. This shift to outpatient treatment implies that more medications are taken with the patient, not medical personnel, exercising quality control. In addition, it is thought to be increasingly difficult for physicians to maintain the continuity and quality of their relationships with patients. Both trends could increase medication errors (ME), particularly among outpatients. ME are "accidental poisoning by drugs, medicaments, and biologicals" and have resulted from acknowledged errors, by patients or medical personnel. US studies of ME have typically been conducted in hospital settings, and have not tracked nationwide trends. We examined all US death certificates between 1983 and 1993 (the latest year available). These certificates indicate cause of death, race, sex, and inpatient/outpatient status.

The figure compares trends in ME with trends in related causes of death. In 1983, 2876 people died from ME. By 1993, this number had risen to 7391, a 2.57-fold increase. (Spearman rank order correlation between year and mortality 0.96; p<0.001.) The only other type of poisoning which showed an appreciable increase was "undetermined poisoning", which rose 2.24-fold. This category is likely to include poisonings from ME in circumstances where the registrar could not rule out homicide or suicide. If the increase in ME deaths results partly from the shift to outpatient care, the increase should be steeper for outpatients than for inpatients. Indeed, outpatient ME deaths rose 8.48-fold (from 172 to 1499), significantly greater than the 2.37-fold increase for inpatients (from 504 to 1195; χ² 293.35; p<0.00001, 1 df). Outpatient deaths from all causes also increased greatly (from 92650 to 191581), though much less steeply than did outpatient ME deaths. In 1983, ME caused one out of every 539 outpatient deaths, versus one out of 1622 inpatient deaths. Thus, in 1983, the proportion of deaths from ME was 3.0 times greater for outpatients than for inpatients (risk ratio 3.0, 95% CI 2.53–3.57; p<0.00001). By 1993, this risk ratio had increased to 6.5, with one out of 131 outpatient deaths from ME, versus one out of 854 inpatient deaths (p<0.00001). Thus, the proportion of deaths from ME has always been particularly large for outpatients, and this proportion has increased substantially in recent years.

The increase in ME deaths cannot be accounted for by increased numbers of prescriptions. ME deaths increased 2.57-fold between 1983 and 1993, while the number of prescriptions increased only 1.39-fold. The increase in ME might result from an increasing willingness to attribute to error deaths that were previously ascribed to natural causes. In an increasingly litigious society, this scenario seems unlikely. The increase in ME is not offset by a decrease in deaths in other poisoning categories, suggesting that the increase does not result from changes in classification practices. Furthermore, the lack of increase in deaths from adverse effects suggests that the ME trend is not due to increased awareness of adverse drug events.

We can uncover some clues about the nature of the increase in ME deaths by examining this increase for each of the nine pharmacological categories listed under medication errors (E850 to E858). For each category, we determined the number of deaths in 1983, in 1993, and the ratio increase (1993 deaths/1983 deaths) over this period:

<table>
<thead>
<tr>
<th>Category</th>
<th>1983</th>
<th>1993</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics, antipyretics, and antirheumatics</td>
<td>851</td>
<td>2098</td>
<td>2.47</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>75</td>
<td>18</td>
<td>0.24</td>
</tr>
<tr>
<td>Other sedatives and hypnotics</td>
<td>43</td>
<td>17</td>
<td>0.40</td>
</tr>
<tr>
<td>Tranquillizers</td>
<td>95</td>
<td>65</td>
<td>0.68</td>
</tr>
<tr>
<td>Other psychotropics</td>
<td>156</td>
<td>315</td>
<td>2.02</td>
</tr>
<tr>
<td>Other central and autonomic nervous system drugs</td>
<td>289</td>
<td>1184</td>
<td>4.10</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>56</td>
<td>43</td>
<td>0.77</td>
</tr>
<tr>
<td>Antifungicides</td>
<td>9</td>
<td>9</td>
<td>1.00</td>
</tr>
<tr>
<td>Other drugs</td>
<td>1302</td>
<td>3642</td>
<td>2.80</td>
</tr>
</tbody>
</table>

The first category (consisting mainly of opiate deaths) and the last category...
Gemcitabine-associated autonomic neuropathy
Arno J Dormann, Thomas Grünewald, Bernd Wigginshaus, Hans Huchzemeyer

Gemcitabine is a new cytidine analogue for the treatment of solid tumours including pancreatic cancer and non-small-cell lung cancer (NSCLC).†,‡ Toxicity appears to be mild, with myelosuppression, raised liver enzymes, and an influenza-like syndrome as the most reported side-effects.³ Renal failure and neurotoxicity are rarely seen. Neuropathy presenting as paresthesia occurs in less than 6% of people treated. We report on a patient who developed autonomic neuropathy in a dosage of 800 mg/m² body-surface area as a 30 min infusion.

A 55-year-old man was diagnosed with NSCLC in January, 1997. He received three cycles of carboplatin and vindesine up to March, 1997. Treatment was stopped because of a good clinical response. In May, 1997, his symptoms worsened again and treatment with gemcitabine in a dosage of 800 mg/m² body-surface area as a 30 min infusion was started at another hospital. After implantation of a permanent venous access, the second and third infusions on days 8 and 15 were administered with a 24 h regimen (150 mg/m²). No other drugs which could have influenced gastrointestinal motility were given.

After the second infusion the patient developed acid regurgitation, difficulties in swallowing, nausea, vomiting, and constipation—all of which worsened after the third infusion.

On admission to our hospital, clinical and laboratory examination was unremarkable except for epigastric discomfort. Further evaluation showed no tumours in the gastrointestinal tract. Barium studies showed prolonged gastric emptying (more than 2 h); colonic transit time was more than 144 hours. Oesophageal 24-h pH-manometry 5 and 15 cm above the lower oesophageal sphincter showed a nearly complete loss of propulsive contractions. Maximum pressure amplitudes during swallowing were less than 20 mm Hg. Marked acid reflux could be detected. Disturbance of autonomous cardiac nerve response was shown by lack of respiratory and circadian variation of heart rate. Nerve-conduction studies were normal. Parenteral nutrition and treatment with cisaprid was started. 4 weeks after stopping gemcitabine, parental nutrition was stopped as symptoms had disappeared.

To the best of our knowledge, this is the first report which describes an association of gemcitabine with autonomic neuropathy. Administration of gemcitabine is usually done by once-weekly infusions over 30 min, which has lower toxicity than a twice-weekly regimen. In some cases a 24 h infusion regimen is used.¹

We cannot exclude a possible association of autonomous neuropathy with the previous administration of carboplatin and vindesine. However, this is highly unlikely because of the considerable time between drug administration and symptoms.

⁵ Pollera CF. More is better but ... how is best: are milligrams over hours better than grams over minutes? The case of gemcitabine (letter). J Clin Oncol 1997; 15: 2112–74.

Medical Clinic, Klinikum Minden, D-32427 Minden (T Grünewald)

Experimental evidence to support ELITE
Lars Christian Rump, Vitus Oberhauser, Eckhard Schwertfeger, Peter Schollmeyer

In the ELITE (Evaluation of Losartan in the Elderly) study¹ patients with heart failure aged 65 and over were treated either with the angiotensin II-receptor blocker, losartan, or with the angiotensin-converting-enzyme (ACE) inhibitor, captopril. Treatment with losartan was associated with an unexpectedly lower mortality than with captopril. The apparent mortality advantage of losartan was due to a reduction in sudden cardiac death, which was suggested to be a result of a more complete suppression of catecholamines at tissue level.¹ Losartan and captopril may have different effects in the heart on local formation of angiotensin II and bradykinin, which both enhance release of cardiac noradrenaline. Losartan may have an unexpected advantage over captopril in the elderly because it is a more specific antagonist of the angiotensin II receptor and the angiotensin-converting-enzyme (ACE). The authors of ELITE offered two explanations for the outcome: even in the presence of captopril, angiotensin II may have been formed by enzymes other than ACE; or bradykinin, metabolised by ACE, may have accumulated. Both events would lead to enhanced release of cardiac noradrenaline.

We tested these hypotheses in human atrial tissue obtained from patients undergoing open-heart surgery for coronary bypass grafting. Tissues were loaded with radio labeled noradrenaline and then the cardiac sympathetic

(consisting mainly of “unspecified drug” deaths) display the largest absolute increases. In relative terms, the largest ratio increase in ME deaths is in the category of “other central and autonomic nervous system drugs” (mainly deaths from anaesthetics).

The increase in ME varies by race and sex. Black males show the largest increase (5:23-fold), followed by white males (2:80-fold), black females (2:27-fold), and white females (1:53-fold). The high-risk groups may be those most likely to receive outpatient treatment.

Our data suggest that medical personnel may need to compensate for changes in medical care by increased vigilance in the delivery and monitoring of medications, especially for outpatients. There is growing concern about the quality and continuity of physician-patient relationships; in the domain of ME, this concern may be justified.

We thank H Phillips, M Schuckit, D Smith, A Steinberg, E Strasser, K Kuritzky, and W Welty, for helpful comments. This paper was supported by grants from the Sutherland Foundation and the Alfred A and Marian E Smith Foundation.

5 IMS America (D P Phillips) and Psychology, University of California at San Diego, La Jolla, CA 92093-0533, USA

644 THE LANCET • Vol 351 • February 28, 1998