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Impact of Restricting Paracetamol Pack Sizes on Paracetamol Poisoning in the United Kingdom

A Review of the Literature

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Abstract

Paracetamol (acetaminophen) is the most common drug taken in overdose in the UK, accounting for 48% of poisoning admissions to hospital and being involved in an estimated 100–200 deaths per year. In 1998, the UK government introduced legislation that reduced the maximum pack size of all non-effervescent tablets and capsules containing aspirin (acetylsalicylic acid) or paracetamol that can be sold or supplied from outlets other than registered pharmacies from 25 to 16 tablets or capsules. This article reviews the literature to determine the effectiveness of the legislation, focusing specifically on paracetamol poisoning. Seventeen studies on this subject were identified. Three studies found reductions in mortality rates; one study found an increase in mortality rates, while one found an initial reduction followed by an eventual increase; three found no significant difference in mortality rates before and after introduction of the legislation. Five studies found reductions in admissions to liver units, three of these finding a reduction in liver transplantation rates; two further studies found no change in liver function tests and rates of paracetamol-induced acute liver injury or failure. Four studies found a sustained decrease in hospital admissions, while two found an initial decrease followed by an eventual increase. One study found a decline in admissions for paracetamol poisoning and an increase in admissions for non-paracetamol poisoning. Sales data are conflicting, with two studies finding no significant difference in paracetamol sales before and after the introduction of the legislation and one reporting a decline. The severity of overdose appears to have decreased since the maximum permitted packet size was reduced, with five studies reporting a reduction in the number of severe overdoses (measured by numbers of tablets ingested, serum paracetamol concentrations and usage of antidotes). Only two studies reported an increase in the number of severe overdoses.

Paracetamol-associated mortality rates, admissions to liver units/liver transplants, hospital admissions and the severity of paracetamol overdose appear to have been decreasing since 1998. However, one study showed that the reductions in mortality and hospital admissions began in 1997; therefore, the contribution of the 1998 legislation to the observed changes is unclear. Most of the studies are based on short-term follow-up so it is difficult to draw any conclusions regarding

long-term trends. Many of the studies were also restricted to relatively small areas of the UK; this, combined with a variety of outcome measures, makes it difficult to distinguish any conclusive trends. The studies also suffer from a lack of comparison and control groups. Some studies do not clearly differentiate between the paracetamol preparations covered by the legislation and those not.

The limited number of studies to date, combined with a variety of outcome measures, make it difficult to determine with accuracy whether or not the legislation has been a success. More long-term studies are needed to fully assess the impact of the legislation.

Deliberate self-poisoning with over-the-counter (OTC) analgesics, particularly paracetamol (acetaminophen), is common in the UK. Indeed, paracetamol accounts for approximately 48% of all poisoning admissions to hospital annually and is involved in an estimated 150 deaths per year.[1] Paracetamol overdose is also the most common cause of acute liver failure in the UK, accounting for up to 60–65% of all cases.[2]

Legislation was introduced in the UK on 16 September 1998 to reduce the pack sizes of all capsules or tablets containing non-effervescent paracetamol or aspirin (acetylsalicylic acid) available from non-pharmacy outlets to a maximum of 16 tablets or capsules per pack[3] (table I). The legislation also stated that pharmacies may sell packets of up to 32 tablets or capsules, that no more than 100 tablets or capsules (or a combination of both) may be supplied at any one time[4] and that specific warnings about the dangers of paracetamol overdose must be printed on packets and leaflets in packets.[5]

Table I. Changes mandated by the legislation introduced in the UK in September 1998 that reduced pack sizes of paracetamol (acetaminophen) and aspirin (acetylsalicylic acid)

The maximum pack size of non-effervescent tablets and capsules containing aspirin or paracetamol or both on the general sale list which may be sold or supplied from outlets other than registered pharmacies was reduced from 25 tablets or capsules to 16, with effect from 16 September 1998[3]
The quantity of non-effervescent tablets and capsules sold or supplied in one container or package by a registered pharmacy shall not exceed 32; the quantity of non-effervescent tablets, capsules or a combination of both sold or supplied to a person at any one time shall not exceed 100[4]
Special warnings are to be included on the packaging of relevant medicinal products containing paracetamol, and in package leaflets accompanying those products[5]

This article aims to review the available literature in order to assess the impact of the legislation over the first 7 years following its introduction.

The electronic databases Medline (1996 to 20 November 2006), CINHAL (1982 to 20 November 2006) and EMBASE (1996 to 20 November 2006) were searched for appropriate literature. Search terms used in the search strategy were 'paracetamol', 'restrict*' and 'legislation' or 'overdose' or 'poisoning'. The inclusion criterion for review was any study set in the UK from 1998 onwards that assessed changes in at least one aspect of paracetamol poisoning in light of the 1998 legislation. The search was limited to the literature title and English language studies only. Bibliographies of review papers were also hand searched for relevant studies. Published responses to the reviews and other literature were also considered where appropriate.

1. Data Summary

One hundred and ninety-nine studies concerning paracetamol poisoning were identified in total (the search strategy was deliberately broad in order to not miss studies and this meant that a large number of irrelevant studies were identified). Abstract titles were searched by hand to identify appropriate studies (any study set in the UK from 1998 onwards that assessed changes in at least one aspect of paracetamol poisoning in light of the 1998 legislation). Thirteen studies[6-18] met the inclusion criteria for review. Four further studies[19-22] were identified from the review of the reference lists of these papers. Three of the 17 studies[6,19,21] had been pub-

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lished as abstracts only. A summary of the reviewed studies is presented in table II; the main findings of the studies are summarised in table III. It was not possible to perform a quantitative analysis or meta-analysis of the data owing to the variability of the studies in terms of the parameters measured and the sizes of the datasets. For this reason it is also difficult to set priority standards from a qualitative point of view; however, from a qualitative point of view, the method is extremely important and therefore we have analysed the methodology of each paper and discussed the impact of this on the interpretation of the results.

2. Mortality

Of the eight studies that considered paracetamol-related mortality,[7-12,20,21] three[7,8,11] found reductions in mortality and one study[9] found an initial reduction followed by an eventual increase; one study[10] reported an overall increase; three studies[12,20,21] found no significant difference. Both studies by Hawton et al.[7,8] showed a reduction in the number of deaths from paracetamol poisoning. In the study published in 2001,[7] a 21% decrease in deaths from paracetamol poisoning was shown in the initial 12 months after the legislation was introduced, and the 2004 study[8] found a 34% reduction in suicide deaths due to paracetamol overdose (when used as a single agent, not in combination with multiple drugs or compounds) over the 2 years following the introduction of the legislation compared with the 2 years before its introduction. No significant difference was found in ibuprofen-related mortality following introduction of the legislation (11 deaths in the 5 years before compared with 13 deaths in the 3 years after).[8] Inglis[9] reported a 45% reduction in deaths due to paracetamol poisoning in 1998, but a subsequent rise occurred over the following 3 years, with mortality reaching pre-restriction levels. Morgan et al.[11] reported a decrease in mortality rates from 4.5 to 2.8 per million between 1997 and 1999 and 3.1 to 2.2 per million between 2001 and 2002. This study also reported that deaths involving compound paracetamol preparations (defined as those paracetamol preparations not covered by the 1998 legislation) remained relatively constant over the study period. This study also found evidence of a decreasing trend in paracetamol-only mortality; this was found to follow overall trends for other poisoning with other drugs, excluding opioids and drugs of misuse. Sheen et al.[12] presented another study based in Scotland; they found no significant difference in mortality rates after introduction of the 1998 legislation. They also found that the paracetamol-related death rate was twice as high in Scotland as in England and Wales (1993–1997). Bateman et al.[10,20] presented two further studies that were performed in Scotland. In the 2003 study[20] they found no significant change in paracetamol poisoning mortality rates between 1990 and 1999, despite an overall decrease in mortality from all causes of poisoning after 1993 and a decline in discharge rates associated with paracetamol poisoning after 1997. In the 2006 study,[10] they reported that the total number of deaths related to paracetamol poisoning decreased slightly after the legislation came into force but subsequently increased between 1999 and 2002; the proportion of poisoning deaths due to paracetamol significantly increased in both males and females between 1995 and 2002. Langford et al.[21] also found no significant change in the number of paracetamol-related deaths in 1998, 1999 and 2002 despite reductions in hospital admissions, admissions to specialist liver units and severe overdoses.

3. Hepatotoxicity

Of the seven studies that considered liver transplants and/or admissions to specialist liver units associated with paracetamol poisoning,[7,8,13,14,18,21,22] five found reductions[7,8,13,18,21] and two showed no change in the occurrence of these events.[14,22] In both studies by Hawton et al.,[7,8] reductions in the number of liver transplants and admissions to liver units were observed. In the 2001 study, a 30% reduction was found in admissions to liver units with hepatotoxicity related to paracetamol poisoning (severity not defined) between October 1996 and September 1999. The total number of liver transplants for paracetamol poison-

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Table II. Summary of reviewed studies on the impact of legislation introduced in the UK in September 1998 that reduced pack sizes of paracetamol (acetaminophen) and aspirin (acetylsalicylic acid)

Study	Study period/setting[a]	Parameters assessed	Outcomes
Bateman et al.[20]	1990–1999; Scotland	Discharge rates, mortality	Overall discharge rates for paracetamol increased until 1997, after which they fell. This change does not seem to have resulted in a major change in paracetamol-related mortality
Bateman et al.[10]	1995–2004; Scotland	Mortality (1995–2003), discharge rates (1995–2004)	Mortality and the proportion of all overdoses that involved paracetamol appeared to have increased since the legislation was introduced
Hawton et al.[7]	1996–1999; England and Wales (mortality), data from five liver units (England) and seven general hospitals (England). UK (sales data)	Mortality, liver transplants and referrals to specialist liver units, numbers of overdoses and tablets taken, blood concentrations of the drugs, prothrombin times, sales data	A significant decrease in mortality attributable to paracetamol or salicylates. A 30% reduction in admissions to specialist liver units. A reduction of 66% in the number of patients receiving liver transplants
Hawton et al.[8]	1997–2001; England and Wales (suicides), data from six liver units (England and Scotland) and five general hospitals (England). UK (sales data)	Mortality, liver transplants and referrals to specialist liver units, nonfatal self-poisoning, sales data	The size of overdoses was significantly reduced with consequent reductions in morbidity and mortality. Some substitution with ibuprofen may have taken place. Both admissions to specialist liver units and the number of liver transplants decreased
Hughes et al.[18]	1995–2002; University Hospitals and the Queen Elizabeth Hospital liver unit, Birmingham, UK	Hospital admissions for paracetamol overdose, admissions to the specialist liver unit with paracetamol-induced hepatotoxicity	A fall in hospital admissions for paracetamol overdose by 31% (360 to 250). Admissions to the specialist liver unit fell by 50% (76 to 38)
Inglis[9]	1991–2002; Scotland	Deaths and emergency admissions	Deaths from paracetamol poisoning fell by 45% in 1998 but subsequently rose over the following 3 years to reach pre-restriction levels. Following the restrictions, the number of poisoning admissions fell by 10% and paracetamol poisoning admissions fell by 14%. Admissions for paracetamol poisonings remained decreased for 2 years but have subsequently increased. The number of admissions for all poisonings remained reduced for 3 years.
Laing et al.[6]	1996–2000; Scottish Poisons Information Bureau, Scotland	Telephone enquiries made to a poisons centre involving paracetamol	Paracetamol enquiries (as a percentage of total enquiries) fell slightly. The proportion of calls regarding patients who had taken more than 16g rose
Langford et al.[21]	1998–1999, 2002; West Midlands, UK	Mortality, hospital admissions, severe overdoses, admissions with paracetamol toxicity to a tertiary liver unit	Hospital admissions fell significantly; admissions for large overdoses (>32 tablets) also fell significantly. The number of patients admitted to the tertiary liver unit fell by a third. Paracetamol-related mortality did not change significantly
Morgan et al.[11]	1993–2002; England and Wales	Mortality, hospital admissions	Mortality rates and hospital admissions due to paracetamol poisoning declined. These changes appear to precede implementation of the legislation

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Table II. Contd

Study	Study period/setting[a]	Parameters assessed	Outcomes
Newsome et al.[22]	1992–2001; Scottish liver transplantation unit, Scotland	Paracetamol-induced acute liver injury, paracetamol-induced acute liver failure, paracetamol-induced acute liver failure meeting poor prognosis criteria	The monthly referral rates for patients with paracetamol-induced liver injury, paracetamol-induced acute liver failure, or paracetamol-induced acute liver failure meeting poor prognosis criteria did not change between December 1992 and August 1998 compared with September 1998 to March 2001
Prince et al.[13]	1995–1999; Freeman liver unit, Newcastle-upon-Tyne, UK. UK transplant special support authority (UKTSSA)	Referrals to specialist liver units, transplantation requests, amount of paracetamol ingested, biochemical data, clinical features	A reduced rate of severe paracetamol hepatotoxicity was reported both locally and nationally
Robinson et al.[14]	1998–1999; five general hospitals in the Belfast area, Northern Ireland	Amount of paracetamol ingested, serum paracetamol concentrations, liver enzyme levels, INR, antidote administration	The estimated quantity of paracetamol ingested was reduced. There was also a reduction in paracetamol concentrations at 4–6 hours and decreased use of antidotes. Liver function tests revealed no changes. No reduction was found in the number of severe paracetamol overdoses
Sheen et al.[19]	1995–2000; Ninewells Hospital, Dundee, Scotland	Paracetamol assay (serum concentration) requests	All requests for paracetamol assays, all positive assays for paracetamol and all potentially hepatotoxic concentrations of paracetamol (>1.3 mmol/L at 4 hours after ingestion) increased from 1995 to 2000; however, these changes were not clinically significant
Sheen et al.[12]	1994–2000; Scotland	Number and annual incidence of paracetamol-related deaths	There were no significant changes in the number and annual incidence of paracetamol-related death following pack size reduction in response to the legislation. The Scottish paracetamol-related death rate was twice as high as in England and Wales
Sheen et al.[16]	1998–2000; UK (sales data)	Sales (mass) of aspirin, paracetamol and ibuprofen	The total mass of paracetamol and aspirin sold over the counter was reduced. The mass of ibuprofen sold was increased, possibly leading to an increase in adverse gastrointestinal events
Thomas and Jowett[15]	1998–1999; Withybush General Hospital, Pembrokeshire, Wales	Hospital admissions for all paracetamol and non-paracetamol overdoses	The number of paracetamol overdoses was found to decline but with an increase in the occurrence of non-paracetamol poisoning. Patients may have switched to alternative agents
Turvill et al.[17]	1995–1999; Royal Free Hospital, London UK	Numbers of overdoses and severe overdoses (those where acetylcysteine or methionine was indicated), benzodiazepine overdose (control)	A 21% reduction in all paracetamol overdoses and a 64% reduction in severe overdoses were observed in the first year after legislation. The frequency of benzodiazepine overdoses remained stable over the study period

a The UK is made up of England, Scotland, Wales and Northern Ireland.

INR = international normalised ratio.

ing was also found to have decreased after legislation, with 66% fewer patients undergoing liver transplantation. The mean peak prothrombin time was also found to have decreased slightly (−2% [95% CI 0 to −4]) [range not defined]. The 2004 study[8] found reductions of approximately 30% in the number of patients admitted to liver units because of paracetamol-induced hepatotoxicity, those listed for liver transplant and who received liver transplantations (a 26% reduction in 1998–2000 and a 34% reduction in 2000–2002 compared with the year before the legislation was introduced). Prince et al.[13] also found a reduction in the incidence of severe paracetamol-related hepatotoxicity on both a local and national scale. Records of patients admitted to the Freeman liver unit (Newcastle-upon-Tyne,

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Table III. Summary of main findings regarding paracetamol (acetaminophen)-related outcomes in reviewed studies

Parameter	Outcomes
Mortality: eight studies[7-12,20,21]	Three[7,8,11] found reductions; one[10] found an increase; one[9] found an initial reduction followed by an eventual increase; three[12,20,21] found no significant difference
Hepatotoxicity: seven studies[7,8,13,14,18,21,22]	Five[7,8,13,18,21] found reductions in the rate of specialist liver unit admission with paracetamol-induced hepatotoxicity; three of these[7,8,13] also found reductions in the number of liver transplants or transplant requests. One[14] found no significant change in liver function tests; one[22] found no change in the rates of paracetamol-induced liver injury, paracetamol-induced acute liver failure, or paracetamol-induced acute liver failure meeting poor prognosis criteria
Hospital admissions: seven studies[9-11,15,18,20,21]	Four[11,18,20,21] reported reductions; one[10] found an increase in adult admissions associated with paracetamol overdose; one[9] showed an initial decline followed by an eventual increase; one[15] found a decline in paracetamol admissions but an increase in admissions for non-paracetamol poisoning
Sales data: three studies[7,8,16]	Two[7,8] reported no significant change in the number of tablets sold before and after the legislation; one[16] reported a progressive decline in the drug mass sold in the 2 years after legislation
Plasma paracetamol concentration: three studies[7,14,19]	One[14] showed a decline (not clinically significant); two[7,19] found no significant difference

UK) and patients registered in the UK for liver transplantation for paracetamol-induced hepatotoxicity between October 1995 and December 1999 were examined. The median monthly number of referrals to the Freeman liver unit fell from 2.5 pre-September 1998 (interquartile range [IQR] 1–4) to 1 (IQR 0–2) after this date ($p < 0.02$). The annual referral rate to the Freeman liver unit fell by an average of 4.5 patients per year between 1995 and September 1998; after September 1998, the referral rate fell by 10 patients per year. The median monthly number of referrals to the United Kingdom Transplant Support Service Authority fell from 3.5 (2.25–5.00) to 2 (1–4) [$p < 0.02$]. The number of referrals had been increasing yearly from 1995 to September 1998 by an average 7.5 patients per year. The observed reductions were not attributable to changes in referral patterns or use of the antidote acetylcysteine. Hughes et al.[18] found an average reduction in admissions to the liver unit with paracetamol-induced hepatotoxicity of 50% per year. Langford et al.[21] found that admissions to a tertiary liver unit for paracetamol-related hepatotoxicity in the West Midlands fell by a third. Newsome et al.[22] presented referral data from the Scottish liver transplantation unit and compared data from patients admitted in 1992–1998 with those admitted in 1998–2001; they found that the monthly referral rates for patients with paracetamol-induced liver injury (3.94–3.57), paracetamol-induced acute liver failure (2.03–1.67) or paracetamol-induced acute liver failure that met the criteria for a poor prognosis (0.97–1.00) did not differ between these two time periods. The study by Robinson et al.[14] also found no reduction in the occurrence of severe ('severe' was not defined) liver failure; this finding was attributed to early administration of the antidote acetylcysteine (time frame not defined). In addition, they reported that there were no significant changes in more sensitive markers such as liver function tests (serum AST levels) and the international normalised ratio (INR).

4. Hospital Admissions

Thomas and Jowett[15] found a reduction in hospital admissions due to paracetamol poisoning, from 45% of total overdoses before the legislation was introduced to 36% after introduction. However, a compensatory increase in non-paracetamol poisoning (antidepressants, antipsychotics and sedatives) was found, and the average time that each patient spent in hospital for paracetamol poisoning or poisoning in general did not change (2.6 days). Inglis[9] reported a 14% reduction in admissions for paracetamol poisoning during the first year of the restrictions, reversing an upward trend in Scotland. This reduction lasted a second year, but admissions

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for paracetamol poisoning subsequently rose by 10% in 2000–2001, and then again by 10% in 2001–2002. Admissions for paracetamol overdose in 2004 made up 36.3% of all poisoning admissions, compared with 26.5% in 1991–1992.

Hughes et al.[18] also found a fall in hospital admissions for paracetamol overdose by an average of 31% per year after introduction of the legislation. Bateman et al.[20] reported that discharge rates for paracetamol poisoning steadily increased between 1990 and 1997 (from 79.1 to 160.2 per 100 000 population in women; and from 56.5 to 118.9 per 100 000 in men). By 1999, rates per 100 000 had fallen significantly to 124.4 in women and 97.2 in men. The data show that the downward trend in paracetamol discharge rates occurred after the 1997 peak; this pattern was not observed for the other groups of drugs studied (antidepressants and opioids). A subsequent study by Bateman et al.[10] showed that both the number of paracetamol-related discharges and the proportion of total discharges that were paracetamol related per quarter increased in adults (aged 20–70 years) between 1996 and 2004. Morgan et al.[11] found that between 1995–1996 and 1997–1998, admissions due to paracetamol poisoning (defined as finished consultant episodes with a primary diagnosis of paracetamol poisoning) increased by 23% for males and 21% for females. Between 1997–1998 and 2001–2002, admissions for males and females declined by 70% and 80%, respectively. The average length of stay following admission was 1.5 days; this remained constant throughout the study period.

Langford et al.[21] found a significant reduction in the number of patients admitted to hospital after paracetamol overdose in both 1999 and 2002 prior to introduction of the legislation; however, the number of admissions in 2002 was found to be slightly higher than in 1999.

5. Sales

Only 3[7,8,16] of the 17 studies reviewed considered sales data. Hawton et al.[7] reported a marked reduction in the mean number of tablets per pack in packs of paracetamol sold to pharmacies in the 12 months after the legislation was introduced when compared with the 12 months before its introduction. A compensatory increase in the number of packets of paracetamol sold was observed, so that the total number of paracetamol tablets sold did not significantly change (approximately 42 million sold in the 12 months before introduction of the legislation compared with approximately 39 million in the 12 months after). The numbers of tablets of preparations containing both paracetamol and salicylates sold did not change significantly following the introduction of the legislation (approximately 15.6 million in the 12 months before legislation compared with 16.2 million in the 12 months after legislation). Similar results were presented in the 2004 study;[8] sales of paracetamol rose after the legislation, so there was little effect on the total number of tablets sold (520 million in 1996–1997, 580 million in 2001–2002), despite the reduction in pack size.

Sheen et al.[16] reported a reduction in the mass of paracetamol sold. In 1999, 48.5% less paracetamol by mass was sold as compared with 1998; in 2000 sales by mass were shown to fall to 40.7% of those in 1998. The total number of paracetamol packs supplied increased from 1998 to 1999 but subsequently decreased back to 1998 levels in 2000. An increase in ibuprofen sales was also reported; ibuprofen sales by mass in 1999 and 2000 were 112% and 173.6%, respectively, of the amount sold in 1998.

6. Severity of Poisoning

Different means of assessing severity were used in the reviewed studies. Measures used include the size of ingestion (number of tablets taken),[6-8,13,14] and the frequency of use of antidotes;[14,17] the studies assessing other measures such as mortality and liver transplantation rates have been discussed above.

In their study published in 2001, Hawton et al.[7] found only a slight decrease (7%) in the mean number of tablets taken per overdose in the 12 months after the legislation was introduced; however, the proportion of overdoses in which ≥32 tablets were taken decreased significantly (17%). The mean

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highest blood paracetamol concentration did not change. A similar pattern was observed in the 2004 study by Hawton et al.,[8] where the numbers of tablets taken in paracetamol overdoses were found to have significantly decreased in the 3 years after the legislation was introduced. In the later of their two studies, Hawton et al.[8] also presented data on ibuprofen; although the numbers of tablets taken per overdose did not significantly change, the total number of ibuprofen overdoses was reported to have increased by 27% in the second and third years after legislation was introduced. Prince et al.[13] also presented data on the amount of paracetamol ingested in patients presenting to a specialist liver unit; between October 1995 and September 1998 the median dose ingested was 35g (interquartile range [IQR] 24–50) and this decreased to 25g (IQR 20–54) after September 1998. Laing et al.[6] presented data from the Scottish Poisons Information Bureau. Their data show that paracetamol enquiries (as a percentage of total telephone enquiries) fell slightly after legislation. However, the proportion of calls regarding ingestions of more than 16g appeared to have risen; little difference was found in the number of patients who had taken more than 8g. Robinson et al.[14] reported significant decreases in the estimated quantity of paracetamol ingested, the number of patients receiving the antidote and the serum paracetamol concentration at 4–6 hours. Turvill et al.[17] defined a severe overdose in their study as any paracetamol overdose where acetylcysteine or methionine was indicated to prevent acute liver injury. They found that between September 1998 and August 1999 there was a 21% reduction in all paracetamol overdoses and a 64% reduction in severe overdoses. The frequency of benzodiazepine overdoses (used as a control) did not change over the study period. Sheen et al.[19] performed another study in Scotland that looked at serum paracetamol concentrations. The study found no significant difference in the occurrence of potentially hepatotoxic levels of paracetamol (defined as >1.3 mmol/L at 4 hours after ingestion) between 1995 and 2000.

Prince et al.[13] presented biochemical data in patients referred to a specialist liver unit between October 1995 and September 1998 compared with between September 1998 and December 1999; their data show a reduction in the number of patients who developed encephalopathy (37 of 95 [39%] to 7 of 22 [32%]) with increases in creatinine levels (median [IQR]: 110 [87–404] to 240 [101–541] μmol/L) and prothrombin time (median [IQR]; 70 [50–109] to 78 [56–104] seconds) and a reduction in arterial pH (median [IQR]; 7.42 [7.37–7.46] to 7.38 [7.35–7.45]).

Laing et al.[6] presented data from the Scottish Poisons Information Bureau. Their data showed a slight reduction in the total number of paracetamol overdoses reported to a poisons centre (694 in 1996–1997 to 546 in 1999–2000). However, the number of cases where paracetamol >8g had been ingested was reported to have increased overall (29 in 1996–1997 to 49 in 1999–2000). In the years 1997–1998 and 1998–1999, the numbers of cases where >8g had been ingested were 67 and 66, respectively, which were more than double the 1996–1997 figure. The number of cases where >16g had been ingested increased overall (17 in 1996–1997 to 21 in 1999–2000).

7. Discussion

7.1 Mortality

The aim of the legislation restricting the size of packs of paracetamol that could be sold OTC [3-5] was to reduce mortality, and so it is surprising that only 8 [7-12,20,21] of the 17 studies identified that examined the effect of this legislation on rates of paracetamol poisoning considered it as an outcome measure. The data are not consistent but appear to suggest that mortality rates may at least be decreasing in England and Wales at least. In Scotland, mortality rates appear to be relatively constant. There have been four large studies in Scotland[9,10,12,20] which have shown no significant decrease in mortality rates since the introduction of the legislation, with two of those studies reporting an eventual increase. There have been three large studies[7,8,11] that have presented data from the office for National Statistics (England and Wales). Morgan et

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al.[11] showed that the decline in mortality from paracetamol self-poisoning in England and Wales began in 1997 – a full year before the legislation came into effect. Therefore, any contribution of the 1998 legislation to reported changes in mortality due to paracetamol poisoning is questionable; this is compounded by the fact that three of the eight studies that examined this outcome[12,20,21] found no significant differences in mortality rates. Interestingly, Hawton et al.[7] used the same mortality data as the Morgan study[11] but failed to note that the decline in mortality began in 1997. Mortality statistics need to be interpreted with some caution, as recording deaths from acute poisoning is not straightforward; where more than one substance (other than alcohol) is implicated in a poisoning death, there is usually no indication on the death certificate as to which substance was principally responsible for the death.[23] Therefore, mortality rates due to paracetamol poisoning, and in particular those where death has occurred with paracetamol preparations covered by this legislation, may be overestimated. It is therefore important to exclude all prescription-only paracetamol preparations from any study in order to obtain an accurate answer as to whether the legislation is succeeding (although, as previously stated, the way in which poisoning deaths are coded may make this difficult to achieve).

It must also be stated that treatment guidelines for paracetamol poisoning have not changed over the review period (although awareness of the correct management of paracetamol poisoning may have improved); nor has there been any national/strategic drive to raise public awareness as to the dangers of paracetamol poisoning.

7.2 Hepatotoxicity

The numbers of liver transplants and/or changes in the number of referrals to specialist liver units would also be expected to be a good indicator of whether the legislation had significantly affected the occurrence of serious paracetamol poisoning. Only 7 of the 17 studies considered this. Of these seven studies, five found reductions in the number of admissions to liver units,[7,8,13,18,21] with three of these finding reductions in the number of liver transplants.[7,8,21] The only national data available are presented by Prince et al.[13] and show reductions both locally in Newcastle-upon-Tyne, UK, and nationally. The localised data are not entirely clear, as referral rates had been falling from 3 years before introduction of the legislation; however, national referrals had been increasing up until September 1998 and then started to decline. Therefore, severe hepatotoxicity has probably reduced overall in the UK, but with some local variation. This point is further emphasised by the Scottish data presented by Newsome et al.[22] showing no change in paracetamol-induced liver injury, paracetamol-induced acute liver failure, or paracetamol-induced acute liver failure meeting criteria for a poor prognosis. In the absence of significant changes in clinical guidelines, this indicates a reduction in the incidence of severe liver failure. Accurate interpretation of the data requires that both the criteria for admissions to liver units and the criteria for liver transplantations have remained constant both across the review period and across the liver units in question. Only Newsome et al.[22] and Prince et al.[13] clarified the criteria used in their studies. Furthermore, many other factors, such as time of presentation or delay in administration of the antidote acetylcysteine, could affect the incidence of paracetamol-related hepatotoxicity and so the observed changes cannot be entirely attributed to the legislation. The study by Robinson et al.[14] is small but is the only one to consider changes in the INR, which is an important indicator of paracetamol-induced hepatotoxicity.

7.3 Hospital Admissions

Hospital admissions due to paracetamol poisoning appear to be decreasing, with four out of seven studies that included this outcome reporting reductions.[11,13,18,20] Again, the reduction seems to be confined to England and Wales; admissions in Scotland appear to have increased beyond pre-legislation levels. This reduction in admissions (at least in England and Wales) reflects both the observed reductions in mortality and hepatotoxicity and sug-

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gests a downward trend in serious or life-threatening paracetamol overdoses. However, there is a lack of comparison with other drugs or indeed overall self-harm; if admissions for these were increasing, as a result of a 'switching' effect, the legislation may inadvertently have had a deleterious effect and be increasing demands on healthcare resources. Only one smaller study assessed whether such an effect had occurred and this showed an increase in overdoses with other agents such as antidepressants, antipsychotics and sedatives.[15]

7.4 Sales

Of the outcomes considered in the reviewed studies, only sales data are presented on a national scale by more than one study.[7,8,16] The data themselves are conflicting; Hawton et al.[7,8] reported no significant change in the number of paracetamol tablets sold before and after the legislation was introduced (in fact their data show an increase from 520 million to 580 million tablets); however, Sheen et al.[16] reported a progressive decline in the mass of paracetamol sold in the 2 years after the introduction of the legislation. Taken as a whole, the sales figures do not support the assumption that the 1998 legislation has led to a decrease in the amount of paracetamol available for ingestion in the average UK home. Sales may not be the most sensitive indicator of the impact of the legislation, as determined patients can simply purchase several packets in different outlets. Whereas Hawton et al.[7] observed an increase in pack sales, which in essence offset the reduced number of available tablets, Sheen et al.[16] observed no significant change in pack sales coupled with a reduction in the mass of paracetamol sold. Therefore, it is very difficult to draw any conclusions from sales data. Furthermore, it is also difficult to determine if the legislation has reduced the amount of paracetamol in the home (i.e. that which is immediately available in the setting of impulsive self-harm).

7.5 Severity of Poisoning

Initial reading of the literature may appear to demonstrate that the severity of overdose seems to have reduced. However, closer analysis of the available data suggests otherwise. Hawton et al.[8] reported a significant reduction in overdose size; however, according to Hawton's data, the mean number of tablets taken during paracetamol overdose (paracetamol alone) in nonfatal self-poisoning has reduced by one tablet (24.3 in the year before legislation, 23.3 in the third year after). The mean number of tablets taken during any paracetamol overdose ('any' not defined) has reduced by only 2.1 tablets (21.1 in the year before legislation, 19.0 in the third year after). Although these reductions may be shown to be statistically significant, they are not of clinical significance; furthermore, the numbers of tablets taken in fatal episodes of self-poisoning were not shown. Prince et al.[13] showed a reduction in the amount of paracetamol ingested; however, the median amount of paracetamol ingested before and after the introduction of the legislation was still substantial and the upper end of the IQR actually increased. Both before and after the introduction of the legislation, the median amount ingested was significantly greater than 16g. The biochemical data presented in this study have some inconsistencies, which the authors do not explain. Although the number of cases of encephalopathy decreased after the introduction of the legislation, the percentage of patients who developed this complication did not significantly change compared with rates prior the legislation; this reflects a downward trend in severe overdoses as a whole. However, the median creatinine level and prothrombin time have actually increased, while the pH has decreased; this is inconsistent with a reduction in encephalopathy or a reduction in severe liver failure.

Laing et al.[6] presents interesting data from the Scottish Poisons Information Bureau. Their data that paracetamol enquiries (as a percentage of total telephone enquiries) fell slightly post legislation. However, the proportion of calls regarding ingestions or >16g appears to have risen; little difference was found in the number of patients who had taken >8g. The data therefore indicate a slight increase in potential severity overall, although the numbers of cases concerned is small.

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Robinson et al.[14] found reductions in the estimated quantity of paracetamol ingested, a reduction in serum paracetamol concentrations and decreased use of the antidote. This indicates a reduction in the severity of overdose (at least in the Belfast area). The follow-up period in this study was very short (January–June 1999). Turvill et al.[17] defined severe paracetamol overdose as being one where acetylcysteine or methionine was indicated to prevent acute liver injury. In the first year after the legislation was introduced (September 1998–August 1999), a 64% reduction in severe overdoses was observed. This indicated a significant reduction in severity of overdose. However, the follow-up period was only 1 year, and the data are presented from only one hospital. Therefore, the data are too limited to determine any definite trends.

The most sensitive marker of risk from acute paracetamol poisoning is a plasma paracetamol concentration taken between 4 and 15 hours after ingestion; this is also a good guide to the dose ingested, as patient-reported histories are often unreliable. Considering this, it is surprising that only three[7,14,19] of the included studies considered this as an outcome measure. The data here are also inconclusive: two studies[7,19] reported no significant difference and one[14] reported a reduction. However, the serum paracetamol concentrations reported in this study are confusing; the peak level observed between January and June 1998 was 80 mg/L, falling to 64 mg/L between January and June of 1999. In patients not at high risk from paracetamol poisoning,[24] these levels are nontoxic at 4–6 hours and do not require treatment with an antidote. Therefore, although serum paracetamol concentrations appear to be falling, in this particular study they were not clinically significant to begin with.

7.6 Data Limitations

The limited number of studies to date combined with a variety of outcome measures make it difficult to determine with accuracy whether the legislation has been a success. There is no single outcome measure that is common to all the identified studies. Many of the reviewed studies are localised and represent only small numbers of hospitals. Only Hawton et al.,[7,8] Prince et al.[13] and Sheen et al.[16] presented data on a national scale; however, Hawton et al.[7,8] and Sheen et al.[16] present national data only for paracetamol sales.

7.6.1 Short Term of Follow-Up

There is also a potential problem with the duration of follow-up; 11 of the 17 studies[6,7,12-17,19-21] reviewed have ≤2 years of follow-up after the introduction of the legislation. The average duration of follow-up across the reviewed studies is approximately 2.3 years. This is not long enough to observe any long-term effects of the legislation and account for potential short-term changes in epidemiology that could be affected by a number of other factors.

7.6.2 Controls

There was also a lack of control or comparison groups in many of the studies. Two studies[8,16] considered ibuprofen as a comparator; however, while this may reveal trends in switching, like paracetamol, ibuprofen is available OTC and so there may be changes in ibuprofen supply and demand over time. Also, as Sheen et al.[16] pointed out, the reduction in the availability of paracetamol may be, in effect, forcing regular users of paracetamol (e.g. those with chronic pain conditions) to switch to ibuprofen. An appropriate control would be any drug or groups of drugs that are available only on prescription and that are not commonly used as drugs of abuse (such as antibacterials or antidepressants). These drugs are not freely available and so would possibly be exempt from the switching effect that may occur with OTC drugs. Only the study by Turvill et al.[17] considered such a control (benzodiazepines) and found no changes in numbers of overdoses with this over the same time period as was considered for paracetamol. However, benzodiazepines may not be the most appropriate control group, as they are frequently used as a drug of abuse. Most of the reviewed studies do not consider overall trends in self-poisoning over the period since the legislation was introduced; this is important, as any observed changes in paracetamol overdoses may just be following overall trends in self-poisoning, as the study by Morgan et al. suggest-

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ed.[11] Therefore, a comparator would be essential in assessing the impact of the legislation, particularly in long-term studies. Data from the Office for National Statistics showing mortality from self-poisoning in England and Wales (figure 1) indicated that paracetamol-related mortality tends to follow a similar trend to that for all intentional poisoning deaths.[25]

7.6.3 Legislation

In many of the studies reviewed, there was a lack of differentiation between paracetamol preparations that were affected by the legislation and those that were not (e.g. those available on prescription only). Data from Morgan et al.[11] show that deaths involving compound paracetamol (defined as preparations not covered by the legislation) remained relatively constant over their study period. Therefore, including all paracetamol preparations would give a negative bias to any study and will reduce the apparent effectiveness of the legislation (it is important to note that many compound paracetamol preparations, including those in which paracetamol is combined with aspirin or a low-dose opioid, are readily available OTC [both general sale list and pharmacy-only preparations] and are covered by the legislation).

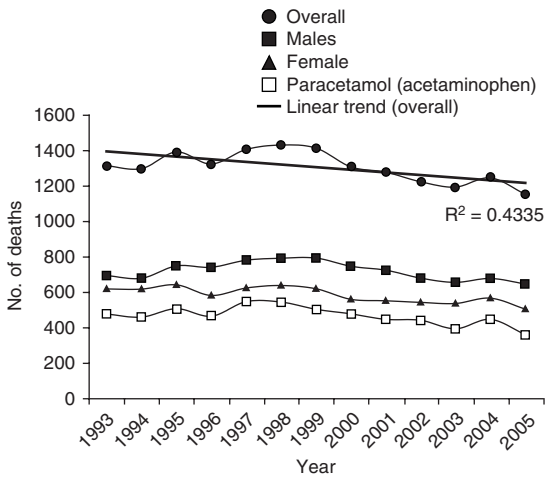

Fig. 1. Mortality from intentional self-poisoning in England and Wales, for the years 1993–2004, according to data from the Office for National Statistics.[25] This data includes intentional self-poisoning by drugs, medicaments and biological substances and poisoning by drugs, medicaments and biological substances with undetermined intent.

There may, however, be difficulties in excluding 'non-legislated' paracetamol from any given data set because of the way that hospital, and particularly mortality, data are coded. Data from poisons centres could be important in facilitating a study that allows an accurate distinction between paracetamol preparations that are covered by the legislation and those that are not.

Several studies[9,11,17,18] have also raised the point that, at around the time of the legislation, paracetamol became available almost exclusively in blister pack form. Turvill et al.[17] indicated this as the main factor in the findings of their audit (a 21% reduction in all paracetamol overdoses and a 64% reduction in severe overdoses were observed in the first year post-legislation). The legislation itself makes no mention of blister packs, and there is no legal obligation for medicines to be packaged in blister packs (MacDonald J, MHRA, personal communication). Although many manufacturers choose to supply medicines in blister packs (mainly to facilitate inclusion of the patient information leaflet) many medicines (including paracetamol and aspirin) are still supplied in bottles. Therefore, blister packs alone cannot be used to explain any observed trends.

Finally, before any changes in the presentation of paracetamol overdose are attributed to the legislation rather than to other factors, it is important to consider whether the legislation is achieving one of its primary goals – to reduce the availability of paracetamol stores in the community and hence the amount of paracetamol immediately available to be ingested in overdose. This is particularly important, as Hawton et al.[26] showed that almost half of all patients that take a paracetamol overdose take paracetamol available in the home. There is currently no published evidence demonstrating that a reduction in the immediate availability of paracetamol has been achieved; also, taken as a whole, the sales data show no dramatic decline in sales of paracetamol. There are also studies[27,28] that have demonstrated that it is still very easy to obtain large amounts of paracetamol from various outlets and therefore, although the total number of tablets being supplied may have been reduced, it is still very easy

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to obtain a potentially toxic dose despite the legislative change.

7.7 Further Considerations

The potential for the restriction of paracetamol to cause patients who self poison to 'switch' to other substances (particularly ibuprofen) is addressed in several of the studies.[8,11,15,16] Switching to ibuprofen, or indeed aspirin, may have considerable public health implications for gastrointestinal disease, as both of these drugs are associated with significant adverse events in therapeutic use. Hawton et al.[8] concluded that some substitution with ibuprofen may have occurred (their data show an increase in the annual number of nonfatal self-poisonings with ibuprofen since the introduction of the legislation) but emphasise that ibuprofen is relatively safe in overdose. It has also been shown that the number of tablets used in ibuprofen overdose has not changed significantly since the legislation was introduced. Therefore, no increase would be expected in the severity of ibuprofen overdose, just an overall increase in the frequency of overdose. Hawton's data also show a decrease in pack sales of ibuprofen since the legislation was introduced. This finding is contradictory to that of Sheen et al.,[16] who not only reported an increase in ibuprofen sales since the legislation was introduced, but also expressed concern about the continuing burden on healthcare resources in terms of gastrointestinal adverse events associated with therapeutic use of ibuprofen. The study by Sheen et al. did not consider renal adverse events, which are well documented with both ibuprofen overdose and therapeutic use.[29,30] Sheen et al.[16] did not consider the relative toxicity of the analgesics. In a published reply to Hawton et al.,[8] Jowett[31] argued that the problem of switching, in the context of self-poisoning, stretches further than ibuprofen and encompasses antidepressants, antipsychotics and sedatives. Therefore, the legislation may have taken pressure off specialist liver units (as the studies by Hawton et al.[8] and others[7,13,18,21] imply) but at the same time have displaced activity to acute medical and high-dependency units and morbidity from liver injury to cardiovascular and/or central nervous system toxicities. The study by Hawton et al.[8] did not consider any other specific groups of drugs or the effects of the legislation on healthcare resources other than specialist liver units. It must also be remembered that an extremely effective antidote for paracetamol poisoning exists (acetylcysteine); such antidotes do not exist for other drugs, emphasising the potential problem if patients self poison with other agents and the impact this could have on the management of patients and health resources.

In a published reply to Hawton et al.,[7] Isbister and Balit[32] raised the argument that the effect of the legislation on paediatric poisoning has not been considered. The legislation itself was introduced to reduce morbidity and mortality with respect to impulsive overdose; intentional self-poisoning is extremely rare in paediatric cases. The majority of accidental paediatric overdoses would be expected to be related to liquid preparations, rather than tablets or capsules. Interestingly, Laing et al.[6] presented data on patients aged ≤12 years. The total number of paracetamol poisoning cases received by the Scottish Poisons Information Bureau in these patients has decreased since the legislation to reduce paracetamol pack size was introduced (267 in 1996–1997 to 137 in 1999–2000).

7.8 Alternative Proposals

In addition to the existing legislation, another proposal could be to make blister packaging for OTC drugs compulsory by law. In theory, this means that the time taken to ingest a toxic quantity of a drug would be longer (on account of having to remove each tablet from the blister pack) and gives the patient more time to reflect on their actions. This could be particularly important, since most intentional poisonings in adults are generally impulsive, often as a reaction to emotional or social crises.[33]

Labelling strategies are already in place, with specific warnings printed on packs. However, this is only likely to reduce accidental overdoses and is less likely to have any impact on intentional self-harm.

Another solution may to widen the availability of paracetamol preparations where the paracetamol is

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dispensed as a fixed combination product with one of its antidotes (acetylcysteine or methionine). One such preparation currently exists in the UK; this contains methionine. However, as most overdoses are impulsive, methionine would need to be added to every paracetamol preparation sold to make any realistic impact. There are, however, potential public health implications of exposing the regular paracetamol-using population to long-term doses of methionine, as its carcinogenic potential has not been evaluated. Some studies also indicate that long-term intake of methionine may be associated with cardiovascular disease.[34] There is concern as to the acute adverse effects of methionine (bad taste, gastrointestinal upset), which may discourage the use of these preparations.[35] There have been no reports of overdose with paracetamol and methionine combinations and therefore there is no evidence that liver damage would be prevented.[34] There would also be the issue of increased costs, both to the pharmaceutical companies and to the consumer.

Another possibility would be to make paracetamol a prescription-only medicine; however, this would substantially increase the workload for primary care services, be an inconvenience to the majority of paracetamol users and increase costs to the health service. It is likely that it would enhance the potential for switching from paracetamol to other analgesics in therapeutic use.

8. Conclusions

It is very difficult to draw any conclusions as to whether the legislation to reduce the paracetamol pack size that is available OTC has had a significant impact on the occurrence of paracetamol poisoning in the UK; not only have the studies to date reached variable conclusions, but there has also been notable variety in the parameters used for assessment. Most of the studies to date have also been localised and represent only relatively small areas of the UK. The follow-up periods of these studies have also generally been very short (just over 2 years at maximum); further studies are needed to fully assess the long-term effects of the legislation.

Some studies have suggested that poisoning with other drugs has increased since the legislation was introduced. For the most part, comparative studies have been restricted to ibuprofen and, as discussed above, other comparisons or controls are required. Alternatives to the legislation have also been suggested, such as packaging paracetamol with one of its antidotes or making the medicine prescription only; however, there are severe limitations to these approaches. Overall trends in self-poisoning have not significantly changed since the legislation to restrict paracetamol pack size was made law. Problems with short-term follow-up mean that further studies are required to fully assess the impact of the legislation, including more data from poisons centres. Taken as a whole, the literature to date provides inconclusive evidence as to whether the legislation to reduce paracetamol pack size in the UK has been effective in reducing paracetamol poisoning.

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