ORIGINAL RESEARCH ARTICLE

Drug Safety 2007; 30 (6): 533-540
0114-5916/07/0006-0533/$44.95/0

Surveillance of Prescription Drug-Related Mortality Using Death Certificate Data

Diane K. Wysowski

Division of Drug Risk Evaluation, Food and Drug Administration, Silver Spring, Maryland, USA

Abstract

Background: The prescription drugs or drug classes that are most frequently associated with death in the US might be identifiable from death certificate data.
Objective: To identify the drugs/drug classes associated with the greatest numbers of deaths in the US that might be considered as possible targets for prevention.
Study design: US vital statistics data were accessed in order to identify International Classification of Diseases (10th Revision) [ICD-10] codes indicating that prescription drugs had caused or contributed to death and diseases with significant drug-related mortality.
Main outcome measure: ICD-10 codes for primarily prescription drugs that were listed as the underlying cause or as 'total mentions' on death certificates and were implicated in ≥1000 deaths in any one year were selected. The annual number of deaths by ICD-10 code was obtained from the Division of Vital Statistics, National Center for Health Statistics. Codes for diseases with significant drug-related aetiologies and involvement in ≥1000 deaths in any one year were also identified and analysed separately.
Results: For the selected ICD-10 codes, a total of 25 031 deaths were listed as having a prescription drug as the underlying cause in 2003, compared with 16 135 in 1999, a 55% increase. Total mentions of these codes increased from 46 523 in 1999 to 72 080 in 2003, also a 55% increase. Most codes involved 'poisonings' (overdose or the wrong substance given or taken in error that is accidental, intentional or with undetermined intent). Drugs associated with poisoning deaths had central nervous system effects. Among the codes associated with specified drug classes, poisonings and accidental poisonings involving narcotics, hallucinogens, psychoactive substances and opioids (other than opium and heroin) were associated with the largest numbers of deaths. Drug-related codes associated with the largest percentage increases in deaths between 1999 and 2003 included poisoning due to methadone (275%); poisoning by other and unspecified antidepressants (primarily selective serotonin reuptake inhibitors) [130%]; and

poisoning by psychostimulants with potential for abuse (amfetamines and drugs for attention deficit hyperactivity disorder) [117%]. Anticoagulants were associated with the largest numbers of deaths with codes involving "adverse effects in therapeutic use". Among diseases with significant drug-related aetiologies, *Clostridium difficile* enterocolitis (associated primarily with antibacterials) had the largest percentage increase in total mentions, with a 203% rise between 1999 and 2003.

Conclusions: Deaths due to overdoses are the most prominent cause of drug-related mortality in death certificate data. Certain drugs and drug classes, especially the opioids (e.g. narcotics, methadone), psychoactive drugs (e.g. antidepressants, amfetamines), anticoagulants and antibacterials (which cause or contribute to *C. difficile* enterocolitis) are associated with large and increasing numbers of deaths and preventive strategies should be considered.

In the US, surveillance of adverse reactions associated with prescription drugs is conducted through the analysis of reports submitted voluntarily by health professionals and consumers to the US FDA. Reports are entered into a database called the Adverse Event Reporting System and are reviewed on an ongoing basis to identify serious adverse drug reactions.[1] Although often used by the FDA for drug risk assessment and subsequent regulation, this surveillance activity is limited by under-reporting that often worsens with a drug's duration of marketing. Because of under-reporting and differential reporting, it is not possible to reliably identify which drugs are most frequently associated with lethal outcomes.

Since all US deaths are required to have death certification that identifies the decedent and the cause(s) of death, and since drug-related deaths can be identified by certain International Classification of Diseases (ICD) codes,[2] access to death certificate data might provide more complete and consistent reporting of deaths associated with prescription drug use. Consequently, to supplement adverse drug reaction surveillance efforts and identify trends in drug-related mortality, annual drug-related mortality data derived from US death certificates were obtained for the period 1999 through 2003. In this study, these data are presented and discussed in terms of their ability to identify drugs associated with large numbers of deaths.

Methods

The annual numbers of deaths, classified according to cause of death using the ICD coding system,[2,3] were obtained from the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention. All US deaths are registered and death certificates are collected from State Health Departments by the Division of Vital Statistics. They are coded and analysed, and mortality data are disseminated. The data are available on request from the NCHS or by internet access (http://www.cdc.gov/nchs/about/major/dvs/mcd/msb.htm) under 'Public Use Documentation'.[3] The current version of the ICD coding system is version 10, which was instituted in the US in 1999.[2] There is a usual lag time in the availability of death certificate data of about 3 years.

Drugs that have played a causative or contributing role in a death should be listed on the death certificate. Certifiers, who are usually physicians, have the option of designating a particular drug (or drugs) as the immediate cause of death, as having contributed to the underlying cause, as the underly-

ing cause or as "other significant conditions contributing to death". The data are then coded by nosologists who assign an appropriate ICD-10 code. Counts by code are available by underlying cause and by total mentions (sum of immediate cause, underlying cause, contributors to the underlying cause and other significant conditions contributing to death). Numbers for underlying cause refer to deaths (one underlying cause per individual), whereas numbers for total mentions refer to codes (not mutually exclusive).

All ICD-10 codes were reviewed and those considered to be drug-related were selected for analysis of data for the years 1999, 2001 and 2003 – the latest year with data available. Only those codes that mentioned prescription (legal) drugs and that were specified as the underlying cause for ≥1000 deaths in any one year or were associated with ≥1000 total mentions in any one year were selected. When a code included both legal and illegal drugs (e.g. narcotics and psychodysleptics [hallucinogens]) or poisoning due to unspecified drugs (which are often a mix of both legal and illegal drugs), the code was included.

Seven codes for diseases in which drugs have been identified as an important or significant aetiological fraction that were associated with ≥1000 annual death certificate total mentions were analysed separately. These disorders included enterocolitis due to *Clostridium difficile* (associated primarily with antibacterial therapy[4-6]); agranulocytosis; aplastic anaemia, unspecified (both caused predominantly by drugs[7-9] including ticlopidine, corticosteroids, antithyroid drugs, sulfonylurea derivatives, allopurinol, gold, phenytoin, carbamazepine and erythromycin); gastric ulcer; duodenal ulcer; and peptic ulcer, site unspecified (all three associated with aspirin and NSAIDs[10,11]); and idiopathic rhabdomyolysis (associated with several drugs, including the frequently-used HMG-CoA reductase inhibitors [statins] alone or in combination with fibric acid derivatives [fibrates],[12,13] and propofol[14,15]). Their ICD-10 codes are described as stated except for idiopathic rhabdomyolysis, which is coded under "other specified disorders of muscle". Other disorders such as heart, liver and renal failure, for which drugs are less prominently involved in the aetiology, were not included; other drug-related disorders (e.g. anaphylactic shock unspecified, idiopathic thrombocytopenic purpura, toxic epidermal necrolysis, angioneurotic oedema, complications of anaesthesia, benign intracranial hypertension, malignant neuroleptic syndrome, etc.) did not meet the criterion of being associated with ≥1000 deaths.

Results

Table I presents the 18 ICD-10 codes that corresponded to prescription drug-related deaths and had ≥1000 annual underlying cause and/or total mentions on death certificates for the years 1999, 2001 and 2003, as well as the percentage change in total mentions from 1999 to 2003. A total of 16 135 death certificates listed the selected ICD-10 codes as the underlying cause of death in 1999 and 25 031 in 2003, a 55% increase (table I). Total mentions of these codes increased from 46 523 in 1999 to 72 080 in 2003, also a 55% increase. Aside from two codes for adverse effects associated with the therapeutic use of anticoagulants and of 'other antineoplastic drugs', all but one of the 16 remaining codes involved 'poisoning' (defined as overdose or the wrong substance given or taken in error that is accidental, intentional, or with undetermined intent). Of the drugs included in the selected poisoning codes, all had effects on the central nervous system (narcotics, opioids, methadone, psychodysleptics [hallucinogens], benzodiazepines, antidepressants, psychostimulants and antiepileptic drugs, sedative hypnotic, antiparkinsonian and psychotropic drugs).

Table I also shows the codes associated with the largest numbers of deaths during 2003. Drugs associated with these codes might be considered as

Table I. Number of deaths with selected ICD-10 codes[a] listed as underlying cause (UC) on death certificates in the US in 1999, 2001 and 2003, total mentions (TM)[a] of these codes and the percentage change in TM, 1999–2003

ICD-10 code	1999		2001		2003		Change in TM
	UC	TM	UC	TM	UC	TM	1999–2003 (%)
F19._ Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances	1 198	5 822	1 265	6 632	1 443	8 311	+43
T40.2 Poisoning by other opioids (includes morphine and codeine)	NA[b]	2 915	NA[b]	3 688	NA[b]	5 162	+77
T40.3 Poisoning by methadone	NA[b]	831	NA[b]	1 559	NA[b]	3 117	+275
T40.4 Poisoning by other synthetic narcotics[c]	NA[b]	772	NA[b]	1 010	NA[b]	1 470	+90
T40.6 Poisoning by other and unspecified narcotics	NA[b]	3 121	NA[b]	3 077	NA[b]	3 306	+6
T42.4 Poisoning by benzodiazepines	NA[b]	1 219	NA[b]	1 699	NA[b]	2 389	+96
T43.0 Poisoning by tricyclic and tetracyclic antidepressants	NA[b]	1 261	NA[b]	1 188	NA[b]	1 325	+5
T43.2 Poisoning by other and unspecified antidepressants[d]	NA[b]	687	NA[b]	1 098	NA[b]	1 582	+130
T43.6 Poisoning by psychostimulants with abuse potential[e]	NA[b]	700	NA[b]	695	NA[b]	1 517	+117
T50.9 Poisoning by other and unspecified drugs, medicaments, and biological substances	NA[b]	9 380	NA[b]	11 104	NA[b]	14 596	+56
X41 Accidental poisoning by and exposure to antiepileptic, sedative hypnotic, antiparkinsonism, psychotropic drugs NEC	671	863	763	943	1 205	1 596	+85
X42 Accidental poisoning by and exposure to narcotics and psychodysleptics (hallucinogens) NEC[f]	6 009	6 887	6 509	7 434	9 231	10 431	+51
X44 Accidental poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances	4 286	5 333	5 525	6 524	7 611	8 741	+64
X64 Intentional self-poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances	1 747	1 827	2 042	2 132	2 241	2 345	+28
Y12 Poisoning by and exposure to narcotics and psychodysleptics (hallucinogens) NEC, undetermined intent	1 425	1 519	1 595	1 679	1 981	2 072	+36
Y14 Poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances, undetermined intent	775	826	875	945	1 270	1 342	+62

Continued next page

Table I. Contd

ICD-10 code	1999		2001		2003		Change in TM
	UC	TM	UC	TM	UC	TM	1999–2003 (%)
Y43.3 Adverse effects in therapeutic use of other antineoplastic drugs	7	1 391	6	1 410	5	1 296	−7
Y44.2 Adverse effects in therapeutic use of anticoagulants	17	1 169	39	1 521	44	1 482	+27
Total	16 135	46 523	18 619	54 338	25 031	72 080	+55

a ICD-10 codes selected as being drug-related and included as the underlying cause in ≥1000 death certificates in any one year or in the total mentions in ≥1000 death certificates in any one year. Tallies for underlying causes based on one code per death; tallies for total mentions are based on a summation of codes (not mutually exclusive).

b By convention, poisoning is not coded as the underlying cause of death.

c T40.4 includes buprenorphine, pethidine (meperidine), and dextropropoxyphene (propoxyphene), among others.

d T43.2 includes selective serotonin reuptake inhibitors, among others.

e T43.6 excludes cocaine and includes amfetamine and methylphenidate, among others.

f X42 includes diamorphine (heroin), cocaine, codeine, lysergide (LSD), morphine, pethidine, narcotic NEC, hallucinogen NEC, hydrocodone, oxycodone (oxycontin) and fentanyl, among others.

ICD-10 = International Classification of Diseases (10th Revision); **NA** = not applicable; **NEC** = not elsewhere classified.

prime targets for prevention of drug-related deaths. Unfortunately, "poisoning by other and unspecified drugs, medicaments, and biological substances" (ICD-10 T50.9) [listed as a cause of death for 14 596 individuals in 2003], and "accidental poisoning by and exposure to other and unspecified drugs, medicaments, and biological substances" (ICD-10 X44) [listed as a cause of death for 8741 individuals] do not indicate which specific drugs were implicated because the certifier did not name the drug(s) on the death certificate. Among the codes associated with identified drug classes, poisonings and accidental poisonings involving narcotics, psychodysleptics, psychoactive substances and opioids (other than opium and heroin) were associated with the largest numbers of deaths.

In terms of relative increases, there was a nearly 275% increase in total mentions of the code for poisoning by methadone between 1999 and 2003, the largest percentage increase for this period (table I). Also of note is the 130% increase in total mentions for deaths due to "poisoning by other and unspecified antidepressants" (primarily the SSRIs) and poisoning by psychostimulants with abuse potential (amfetamines and drugs for attention deficit hyperactivity disorder) [117%].

Table II shows the number of deaths for diseases in which drugs have been identified as having an important or significant aetiological role. The largest percentage increase in total mentions of codes for these deaths between 1999 and 2003 was for *C. difficile* enterocolitis (+203%); prior antibacterial use is the primary risk factor for *C. difficile*-associated diarrhoea.[5,6] Although the number of deaths from *C. difficile* enterocolitis increased considerably, deaths related to aplastic anaemia unspecified, agranulocytosis and gastric, duodenal and peptic ulcer, site unspecified, while continuously large in number, registered declines over the period.

Table II. Number of deaths for selected diseases[a] listed as the underlying cause (UC) on death certificates in the US in 1999, 2001 and 2003, total mentions (TM) of these codes and the percentage change in TM, 1999–2003

ICD-10 code	1999		2001		2003		Change in TM
	UC	TM	UC	TM	UC	TM	1999–2003 (%)
A04.7 Enterocolitis due to *Clostridium difficile*	793	1 545	1 332	2 316	2 776	4 681	+203
D61.9 Aplastic anaemia, unspecified	1 023	4 572	1 043	4 304	905	4 203	−8
D70 Agranulocytosis	338	2 789	351	2 565	359	2 631	−6
K25 Gastric ulcer	1 333	2 881	1 277	2 639	1 154	2 344	−19
K26 Duodenal ulcer	1 476	2 888	1 544	2 806	1 324	2 364	−18
K27 Peptic ulcer, site unspecified	1 758	5 810	1 631	5 015	1 379	4 066	−30
M62.8 Other specified disorders of muscles (includes rhabdomyolysis, [idiopathic])	417	1 225	503	1 454	505	1 553	+27
Total	7 138	21 710	7 681	21 099	8 402	21 842	+0.6

a ICD-10 codes were selected in which drugs are an important aetiologic fraction of the disease and with which the number of deaths with underlying cause or total mentions on death certificates was ≥1000. The aetiologic fraction attributable to drugs is considerable for enterocolitis due to *C. difficile*, agranulocytosis, and aplastic anaemia, unspecified, but is less so for gastrointestinal ulcers and idiopathic rhabdomyolysis. Tallies for underlying cause are based on one code per death; tallies for total mentions are based on a summation of codes (not mutually exclusive).

ICD-10 = International Classification of Diseases (10th Revision).

Discussion

To determine trends and assess progress in preventing deaths related to prescription drugs, vital statistics data were obtained and drug-related codes associated with ≥1000 deaths annually were investigated. Although the media often focus on the "adverse events in therapeutic use" of marketed drugs, only two codes from this category (anticoagulants and "other antineoplastic drugs") met the criterion of being associated with ≥1000 deaths per year, while the codes that accounted for the largest share of deaths concerned poisoning (overdose) deaths in which opioids and psychoactive drugs were implicated.

Despite the usefulness of death certificates in providing national trend data, there are many limitations of their use. With rare exceptions (e.g. methadone), ICD codes do not specify individual drugs, so an important limitation is the inability to obtain specific drug names as causes on death certificates.[16] This is due to the structure of the codes that group together drugs or drug classes, so that when drugs are named on death certificates they are not singularly tallied; their identification is only available from the actual certificates. Drug names also are absent from death certificates because of certifiers' under-attribution of drug-related deaths. Certifiers of death may not recognise a drug as a cause of, or as contributing to, a patient's death, and when they do, they sometimes write 'adverse drug reaction' without providing the name of the drug on the death certificate. Furthermore, toxicological data are often unavailable at the time of death certification although death certificates can be amended to include subsequent information.

Deaths from diseases that are not always drug-related (e.g. *C. difficile* enterocolitis, agranulocytosis and aplastic anaemia, gastrointestinal ulcer codes) were included because drugs have been identified as a significant aetiological fraction in these diseases. However, gastrointestinal ulcers can be caused by infection with *Helicobacter pylori*[17] and rhabdomyolysis can be caused by illegal drugs, al-

cohol and exercise.[18] However, a much lower incidence of acute renal failure, and therefore death, has been reported with rhabdomyolysis associated with exercise,[19] and the median age group of death of 75–79 years[3] is more consistent with a drug-related aetiology than with other risk factors. Without the actual certificates (or data mining of them) it is not possible to determine how frequently drugs are mentioned for these and other disorders with significant drug-related causes.

Although an attempt was made to restrict the data to prescription drugs, the structure of ICD codes mixes legal and illegal drugs together (e.g. narcotics and psychodysleptics) and this made such restriction difficult. Many deaths could be the result of mixing drugs and/or alcohol together and many could be due to intentional overdose. Furthermore, calculation of rates by drug or drug class was not able to be performed because of the lack of specific drug names and lack of drug use denominator data. However, the trend in the dispensing of prescription drugs during this period was an increase (33% increase between 1998 and 2003),[20] as was that for the sales of opioids,[21] so prescribing increases probably account, in part, for the overall increase in the numbers of deaths. This also appears to be the case with methadone, in which prescriptions have increased with the increase in deaths.[21-23] Nevertheless, the 55% increase in deaths for the selected ICD-10 codes during this 5-year period exceeds the predicted percentage increase based on overall prescription drug dispensing.

The increases reported herein are similar to results from other studies that have shown recent upward trends in drug overdose deaths.[21-25] In New Mexico, the population rate of unintentional prescription drug overdose deaths increased by 179% from 1994 to 2003.[24] Of all deaths caused by prescription drugs in this State, 77% were caused by opioid painkillers, 34% by tranquillisers and 26% by antidepressants. Recent reports in the medical literature and news media of an increase in methadone-related diversion, abuse and deaths[21-23] are also consistent with the large percentage increase nationally in methadone overdose deaths reported herein. According to a recently available study by the NCHS using 2004 death certificate data,[26] the number of deaths associated with methadone use in the US rose to 3849, a 390% increase from the number in 1999. Other prescription drugs, such as oxycodone (oxycontin) and fentanyl, (aggregated with other drugs in ICD-10 code X42, accidental poisoning by and exposure to narcotics and psychodysleptics [hallucinogens]) have also attracted reports and media attention about abuse and death associated with overdose.[21,25,27-29] Also, the large percentage increase in deaths from *C. difficile* enterocolitis is consistent with recently published studies indicating increases in the severity of this disorder.[4-6,30]

Surveillance of drug-related deaths would be aided if physician certifiers included specific drug names on death certificates when drugs have caused or contributed to death. Surveillance also could be improved if data mining of death certificates for individual drugs was performed. Based on death certificate data, certain drugs and drug classes, especially the opioids (e.g. narcotics, methadone), psychoactive drugs (e.g. antidepressants, amfetamines), anticoagulants and drugs causing or contributing to *C. difficile* enterocolitis (primarily antibacterials) are related to large and increasing numbers of deaths and should be considered in strategies for the prevention of such deaths.

Acknowledgements

The views expressed are those of the author and do not necessarily represent the official position of the US FDA. No sources of funding were used to assist in the preparation of this manuscript. The author has no conflicts of interest that are directly relevant to the content of this manuscript.

References

1. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. Arch Intern Med 2005; 165: 1363-9
2. International Statistical Classification of Diseases and Related Health Problems, Tenth revision, (ICD-10). Geneva: World Health Organization, 1992: volume 1
3. Public use data tape documentation. Multiple cause of death for ICD-10 1999-2003 data. Hyattsville (MD): U.S. Department of Health and Human Services, Public Health Service, National Center for Health Statistics, 1999-2003 [online]. Available from URL: http://wonder.cdc.gov/wonder/sci_data/mort/mcmort/type_txt/mcmort03/ControlTotalTable1.pdf [Accessed 2007 Apr 27]
4. Pepin J, Valiquette L, Alary M-E, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1999 to 2003: a changing pattern of disease severity. CMAJ 2004; 171: 466-72
5. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med 2005; 353: 2442-9
6. Bartlett JG, Perl TM. The new *Clostridium difficile* - what does it mean? N Engl J Med 2005; 353: 2503-5
7. Kaufman DW, Kelly JP, Levy M, et al. The drug etiology of agranulocytosis and aplastic anemia: monographs in epidemiology and biostatistics, volume 18. New York: Oxford University Press, 1991
8. Ibanez L, Vidal X, Laporte JR. Population-based drug-induced agranulocytosis. Arch Intern Med 2005; 165: 869-74
9. Shapiro S, Issaragrisil S, Kaufman DW, et al. Agranulocytosis in Bangkok, Thailand: a predominantly drug-induced disease with an unusually low incidence. Aplastic Anemia Study Group. Am J Trop Med Hyg 1999; 60: 573-7
10. Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. Ann Intern Med 1988; 109: 359-63
11. Lassen A, Hallas J, de Muckadell OB. Complicated and uncomplicated peptic ulcers in a Danish county 1993-2002: a population-based cohort study. Am J Gastroenterol 2006; 101: 945-53
12. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin-gemfibrozil combination therapy. JAMA 1990; 264: 71-5
13. Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004; 292: 2585-90
14. Cannon ML, Glazier SS, Bauman LA. Metabolic acidosis, rhabdomyolysis, and cardiovascular collapse after prolonged propofol infusion. J Neurosurg 2001; 95: 1053-6
15. Wysowski DK, Pollock ML. Reports of death with use of propofol (Diprivan) for nonprocedural (long-term) sedation and literature review. Anesthesiology 2006; 105: 1047-51
16. Wysowski DK, Nourjah P. Analyzing prescription drugs as causes of death on death certificates. Public Health Rep 2004; 119: 520
17. Dunn BE, Cohen H, Blaser MJ. *Helicobacter pylori*. Clin Microbiol Rev 1997; 10: 720-41
18. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine 2005; 84: 377-85
19. Sinert R, Kohl L, Rainone T, et al. Exercise-induced rhabdomyolysis. Ann Emerg Med 1994; 23: 1301-6
20. Wysowski DK, Governale LA, Swann J. Trends in outpatient prescription drug use and related costs in the US. Pharmacoeconomics 2006; 24: 233-6
21. Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006; 15: 618-27
22. Cicero TJ, Inciardi JA. Diversion and abuse of methadone prescribed for pain management. JAMA 2005; 293: 297-8
23. Dart RC, Woody GE, Kleber HD. Prescribing methadone as an analgesic. Ann Intern Med 2005; 143: 620
24. Mueller MR, Shah NG, Landen MG. Unintentional prescription drug overdose deaths in New Mexico, 1994-2003. Am J Prev Med 2006; 30: 423-9
25. Cone EJ, Fant RV, Rohay JM, et al. Oxycodone involvement in drug abuse deaths: a DAWN-based classification scheme applied to an oxycodone postmortem database containing over 1000 cases. J Anal Toxicol 2003; 27: 57-67
26. Fingerhut LA. Increase in methadone-related deaths: 1999-2004 [online]. Available from URL: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/methadone1999-04/methadone1999-04.htm [Accessed 2007 May 7]
27. Tharp AM, Winecker RE, Winston DC. Fatal intravenous fentanyl abuse: four cases involving extraction of fentanyl from transdermal patches. Am J Forensic Med Pathol 2004; 25: 178-81
28. Barrueto F Jr, Howland MA, Hoffman RS. The fentanyl tea bag. Vet Hum Toxicol 2004; 46: 30-1
29. Meadows M. Proper use of fentanyl pain patches. FDA Consumer magazine March-April, 2006
30. Wysowski DK. Increase in deaths related to enterocolitis due to Clostridium difficile in the United States, 1999-2002. Public Health Rep 2006; 121: 361-2

Correspondence: Dr *Diane K. Wysowski*, Division of Drug Risk Evaluation, Food and Drug Administration, White Oak, Building 22, Room 3424, 10903 New Hampshire Ave., Silver Spring, HFD-430, MD 20993, USA.