Drug and Alcohol Review (July 2007), 26, 405–410

informa
healthcare

Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records

AMY E. GIBSON & LOUISA J. DEGENHARDT

National Drug and Alcohol Research Centre, University of New South Wales, Australia

Abstract

Introduction and Aims. *The aim of this study was to compare the mortality associated with oral naltrexone, methadone and buprenorphine in opioid dependence treatment, employing a retrospective data analysis using coronial and prescription data.* ***Design and Methods.*** *The number of deaths were identified through national coronial data and number of treatment recipients were estimated from 2000 to 2003 prescriptions and restricted medications data. Mortality rates were expressed as deaths per number of treatment episodes and per person-years at high and low risk of fatal opioid overdose.* ***Results.*** *Thirty-two oral naltrexone, one buprenorphine and 282 methadone-related deaths were identified. Mortality rates in the highest risk period in deaths per 100 person-years were 22.1 (14.6–32.2) for oral naltrexone following treatment cessation and 3.0 (2.3–3.9) for methadone during treatment induction. Rates in the lowest risk period in deaths per 100 person-years were 1.0 (0.3–2.2) during oral naltrexone treatment and 0.34 (0.3–0.4) during post-induction methadone treatment. The relative risk of death for oral naltrexone subjects was 7.4 times (high-risk period,* $p < 0.0001$*) or 2.8 times (low-risk period,* $p = 0.055$*) that of methadone subjects.* ***Discussion and Conclusions.*** *This is the first comparison of mortality associated with these three pharmacotherapies for opioid dependence. The risk of death related to oral naltrexone appears higher than that related to methadone treatment.* [Gibson AE, Degenhardt LJ. Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug Alcohol Rev* 2007;26:405–410]

Key words: buprenorphine, methadone, mortality, naltrexone, opioid dependence.

Introduction

Opioid dependence is a chronic, relapsing disorder [1,2] associated with elevated mortality risk, with death most commonly from opioid overdose [2–5]. The mortality rate among untreated opioid-dependent individuals has been estimated at 0.9 per 100 person-years [6]. Reducing this mortality risk is an important aim of opioid dependence treatment. However, users often cease treatment; and that mortality risk will differ during and following the treatment episode depending upon the nature of the treatment modality. The current study compares mortality risk related to three pharmacotherapies for opioid dependence: naltrexone, buprenorphine and methadone.

The range of maintenance pharmacotherapy treatments available for opioid dependence include opioid antagonists such as naltrexone, partial opioid agonists such as buprenorphine and full opioid agonists such as methadone. For several decades, methadone has been the primary drug for opioid maintenance pharmacotherapy [5] and plays an important role in retaining patients in treatment, improving health, reducing criminal activity and decreasing heroin and other drug use [7]. Buprenorphine is a more recently developed medication that is being prescribed increasingly in many countries [8,9] and is similarly effective to methadone in terms of retention and suppression of heroin use [10]. Naltrexone, in contrast, has been available for many years but has remained little-used due to low interest among opioid-dependent individuals and poor compliance with treatment [5,11,12]. No significant benefit of naltrexone over placebo has been found in terms of retention, side effects or relapse to heroin use [13].

Each of these treatments bears some mortality risk, which differs over the course of treatment due to the different mechanisms of drug action. Methadone provides some cross-tolerance to opioids, so once inducted into treatment recipients have a lower overdose mortality rate than untreated opioid-dependent

Amy E. Gibson MPH BSc (Hons) BA, Senior Research Officer, National Drug and Alcohol Research Centre, University of New South Wales, Australia, Louisa J. Degenhardt PhD, MPsychol (Clinical), BA (Hons), Senior Lecturer, National Drug and Alcohol Research Centre, University of New South Wales, Australia. Correspondence to Amy Gibson, NDARC, UNSW, Sydney, NSW, Australia 2052.
E-mail: amy.gibson@med.unsw.edu.au

Received 17 July 2006; accepted for publication 18 December 2006.

ISSN 0959-5236 print/ISSN 1465-3362 online/07/040405–06 © Australasian Professional Society on Alcohol and other Drugs
DOI: 10.1080/09595230701373834

subjects [14,15]. During induction, however, the risk of fatal opioid overdose is high, with one study estimating 7.4 deaths per 100 patient-years in the first 2 weeks of methadone treatment, compared to 0.07 deaths per 100 patient years beyond 2 weeks [16], and another study finding that 21% of deaths in methadone treatment occurred during the first week [17]. Death is caused primarily by respiratory failure or complications arising from opioid overdose, and methadone is usually detected in post-mortem toxicology [18,19].

Buprenorphine has a longer mechanism of action than methadone, with a flatter dose–response curve, so that high doses prolong but do not increase the peak effects [20], making subjects less likely to experience a fatal overdose [21]. The great majority of all fatal overdoses have involved the concomitant administration of other respiratory-depressant drugs, usually benzodiazepines and/or alcohol [22], although some buprenorphine-only deaths have been reported [23]. Opioid overdose deaths in France have decreased substantially since the introduction of buprenorphine [24] and the mortality rate attributed to buprenorphine treatment has been estimated at 0.24 per 1000 patients [25].

Naltrexone is an opioid antagonist, used primarily as a maintenance drug to aid opioid abstinence. Overdose rates associated with naltrexone have been less well documented than with methadone and buprenorphine, perhaps because the greatest risk occurs after the cessation of treatment. While compliant with naltrexone, the effects of any opiates administered are blocked or reduced substantially [26]. The primary cause of naltrexone-related death is by opioid overdose after cessation of naltrexone treatment [27]. Such deaths are unlikely to have naltrexone detected in post-mortem toxicology, and only the mention of recently ceased (or non-compliant) naltrexone treatment identifies the death as naltrexone-related. Less commonly recognised causes of naltrexone-related death include fatal opioid overdose during naltrexone treatment [27], and death from a severe adverse reaction to naltrexone [28].

There has been limited comparative work examining mortality rates across these three pharmacotherapies for opioid dependence. Higher rates of opioid overdose (mainly non-fatal) in naltrexone subjects compared to methadone and buprenorphine subjects was noticed in a group of Australian studies [29]. Subjects leaving naltrexone treatment had an overdose rate eight times that of subjects leaving agonist treatment, and naltrexone recipients were six times more likely to experience an overdose out of treatment than in treatment. Three of the 27 overdoses proved fatal [29]. Another Australian study reported higher rates of non-fatal overdose in naltrexone recipients compared to opioid agonist treatment [30].

There has been no epidemiological work completed to examine rates of mortality related to these treatments as used in routine clinical practice. This report uses coronial data to quantify and directly compare the mortality associated of oral naltrexone with that of buprenorphine and methadone treatment for opioid dependence in Australia, including deaths both during and after an episode of treatment. This will provide the first estimate of the mortality rate related to oral naltrexone treatment in Australia.

This study aims to:

(1) estimate the number of people receiving pharmacotherapy for the treatment of opioid dependence;
(2) estimate the number of deaths related to these treatment forms; and
(3) estimate mortality rates according the number of treatment episodes, and among periods of low and high risk.

Methods

The number of deaths related to naltrexone, buprenorphine and methadone were determined by keyword searches of the National Coronial Information System (NCIS). The NCIS is a regularly updated electronic database allowing access to all coronial cases in Australia [31]. Between 2000 and 2003, inclusive, an estimated 88% of a total of 66 659 coronial cases nationally were closed coronial cases (cases no longer under coronial investigation), and so were able to be used in this analysis (NCIS, unpublished data).

National registration data were used for the number of buprenorphine and methadone treatment episodes. As naltrexone is only available privately for the treatment of opioid dependence and registration data are not kept, the number of private prescriptions of oral naltrexone and expert clinical and research experience [21] of the typical naltrexone treatment retention were used to calculate the number of naltrexone treatment episodes. Mortality relating to unregistered forms of naltrexone, such as depot formulations, was not considered here.

Mortality rates were calculated using: (a) a crude rate of deaths per 1000 treatment episodes and (b) a stratified rate of deaths per 100 person-years at high or low risk of death. All deaths were classified as occurring in either the high- or low-risk period of death; high-risk period deaths occurred if the date of death was recorded as being within 2 weeks after the cessation of naltrexone treatment episode or in the first week of methadone or buprenorphine treatment.

Deaths during naltrexone treatment or after the first week of methadone or buprenorphine treatment were classified as occurring during the low-risk period. Deaths where the timing was uncertain were classified in the low-risk period of death and deaths occurring

more than 2 weeks post-treatment cessation were not considered to be related to the treatment. Treatment episodes were considered to have ended if the patient had formally left treatment at the time of their death. Using a mortality rate of deaths per person-years at risk reduces any bias caused by differing treatment retention between the three pharmacotherapies, as retention has been shown to be longer in methadone and buprenorphine than in naltrexone [21].

The significance of the difference in mortality rates was tested using Poisson regression models using SAS version 8.2.

Results

Searches of the NCIS revealed 282 methadone, one buprenorphine and 32 oral naltrexone-related deaths during 2000–03 in Australia. Of these 258, one and 15 deaths, respectively, met the criteria for 'known' methadone-, buprenorphine- and naltrexone-related deaths. This includes where the drug in question is mentioned as a cause of death in the coronial or autopsy document, an opioid overdose within 2 weeks of cessation of treatment or an opioid overdose where the person is known to be in current treatment with the drug in question. A more detailed description can be found in [32]. According to national records, an estimated 102 615 episodes of methadone and 49 948 episodes of buprenorphine treatment occurred in Australia during that time. A total of 6337 private naltrexone prescriptions were filled during 2000–03, each providing medication for 1 month. Assuming mean treatment retention of 2 months, the number of oral naltrexone treatment episodes during this time was 3169.

The crude estimated mortality rate was 2.7 deaths per 1000 episodes for methadone, 0.02 per 1000 treatment episodes for buprenorphine and 10.1 per 1000 treatment episodes for naltrexone. Naltrexone subjects had 3.7 times the mortality risk compared to methadone subjects, a highly significant difference ($p < 0.0001$). With 95% confidence, the true relative risk falls between 2.5 and 5.2 times higher than methadone treatment.

Methadone treatment was associated with a mortality rate of 3.0 per 100 person-years during the high-risk period (first week of treatment) and 0.34 per 100 person-years during the period of low risk (the remainder of the treatment episode). Buprenorphine mortality rates were not calculated using this method due to the low number of deaths detected. Naltrexone was associated with a mortality rate of 22.1 per 100 person-years during the period of high risk (2 weeks post-treatment), and one per 100 person-years during the period of low risk (during treatment). Mortality estimates and their 95% confidence intervals are included in Table 1.

Naltrexone subjects 2 weeks post-treatment (high-risk period) had 7.4 times the risk of dying than methadone subjects in their first week of treatment (high-risk period). This risk was highly significant ($p < 0.0001$, 95% CI: 4.6–11.5). Naltrexone subjects during treatment (low-risk period) have 2.8 times the risk of dying than methadone subjects in the post-induction treatment period (low-risk period). This risk approaches significance ($p = 0.055$, 95% CI: 1.3–5.7).

Discussion

Deaths related to methadone, buprenorphine and naltrexone have occurred in Australia, and clear differences in risk were observed. Whether estimated as deaths per 1000 treatment episodes or per 100 person-years of high risk, the mortality rates for naltrexone treatment were significantly higher than those for methadone treatment ($p < 0.0001$). Our methadone mortality rate of 3.0 deaths per 100 patient-years is comparable to the 7.4 deaths per 100 patient-years obtained by other researchers [16] in the initial high-risk period of treatment. Our buprenorphine mortality rate of 0.02 per 1000 episodes can be compared to the French estimate of 0.24 per 1000 patients [25] and 2.5 per 1000 patients in the NEPOD studies [29]. As only a single death in buprenorphine patients was noted in both this and the NEPOD studies, caution should be used when comparing rates and significant differences in buprenorphine mortality

Table 1. *Mortality rates per 1000 treatment episodes and per 100 person-years of exposure (stratified into periods of high and low risk of death), Australia 2000–2003*

		Deaths per 100 person-years of exposure	
	Deaths per 1000 treatment episodes	High risk period	Low risk period
Methadone	2.7 (95% CI: 2.4, 3.1)	3.0 (95% CI: 2.3, 3.9)	0.34 (95% CI: 0.3, 0.4)
Buprenorphine	0.02 (95% CI: 0.0005, 0.1)	Not calculated	Not calculated
Naltrexone	10.1 (95% CI: 6.9, 14.3)	22.1 (95% CI: 14.6, 32.2)	1 (95% CI: 0.3, 2.2)

to methadone and naltrexone treatment were not tested.

The naltrexone-related mortality rate during treatment (one per 100 person-years) is very similar to the overdose mortality rate for non-treated opioid dependent subjects of 0.9 per 100 person-years [6], suggesting that naltrexone offers little benefit in terms of mortality risk. In the high-risk period after treatment cessation, naltrexone-related mortality increased to 22.1 per 100 person-years, a rate clearly elevated compared both to other pharmacotherapies and also to active, dependent heroin use [6]. The NEPOD studies reported a naltrexone mortality rate of 4.8 deaths per 100 person-years after treatment cessation [29]. The lower mortality rate in these studies could be partially a reflection of standardised treatment protocols and intensive monitoring present in the research rather than the general clinical setting. Mortality rates following naltrexone treatment can also be compared to mortality in other reportedly opioid-abstinent situations, such as shortly after release from prison. The rate of five deaths per 1000 prisoner releases in the 2 weeks following release in a Scottish study [33] is lower than our crude estimate of 10.1 deaths per 1000 treatment episodes for naltrexone.

The mortality rates we have found are plausible given both the pharmacology of these drugs and previous research [16,29,30,34]. Naltrexone is a treatment that reduces tolerance to opioids, and reduces opioid effects during treatment. Buprenorphine and methadone, in contrast, provide tolerance to all other opioids during treatment. It is not surprising, then, that there is a higher potential for more deaths to occur post-naltrexone treatment.

Retention in naltrexone treatment is poor: approximately one-third of subjects remain in naltrexone treatment after 3 months [12,35]. The mortality risk associated with naltrexone treatment is of particular concern, considering the dangerous combination of poor naltrexone compliance and sporadic heroin use [36,37].

It should be noted that naltrexone treatment may be a useful option in some well-motivated patient subgroups, such as medical professionals [27,38], with strong imperatives to remain abstinent. However, these subgroups represent the minority of dependent opioid users, and successful abstinence attempts are not the norm, even in the well-motivated subjects [39].

Implant technologies have been proposed as alternative methods for delivering naltrexone [40–44]. These are not registered for use in Australia, and due to a lack of data on the number of naltrexone implant recipients this study was unable to make estimates of mortality rates related to naltrexone implants. However, three naltrexone implant-related deaths were identified in the NCIS over the same period, suggesting that naltrexone implants carry a mortality risk. Naltrexone implant deaths may be more difficult to identify than oral naltrexone deaths due to poor reporting of the presence of an implant at autopsy [45]. Future work needs to examine this issue carefully.

Limitations

Previous reports of naltrexone-related deaths [28,29,34,36,46] have been accompanied by concerns about the inability to monitor overdose deaths after naltrexone treatment cessation [37]. Both inadequacies in the data and assumptions in calculating the mortality rates have the potential to bias, in particular, our estimates of naltrexone mortality. First, identifying naltrexone-related deaths is difficult. Not only do naltrexone-related deaths rarely have naltrexone detected in post-mortem toxicology, they rely on a past episode of naltrexone treatment being recorded in coronial databases, something not conducted systematically in Australia. We were limited to keyword searching of the coronial database and so relied on correct spelling of the search terms in the files. For this reason we believe we may have underestimated the number of naltrexone-related deaths using the NCIS.

Secondly, we have assumed that only private prescriptions of naltrexone were for opioid dependence treatment. If we assume that half of opioid-dependent patients were also alcohol-dependent [47] and so eligible for a public prescription, the number of treatment episodes would be increased by 50%, reducing the naltrexone mortality estimate by a factor of two. Thirdly, the mean length of a naltrexone treatment episode was estimated by a number of clinical experts. Longer mean retention in treatment would elevate the naltrexone-related mortality.

Our selection of the first week of methadone treatment as the period of high risk was influenced by the limitations of the data and previous research [17]. This does not necessarily imply that the high-risk period does not extend to the first 2 weeks of treatment, as discussed by other authors [16,48]. No additional deaths were noted in the first 2 weeks of methadone treatment compared to the first week. This may be a reflection of a certain bias in the NCIS: the further separated a death was from the commencement of treatment, the less likely the timing of treatment was noted as salient in the coronial records.

Estimates of deaths associated with the three pharmacotherapies include deaths occurring among people using diverted medication. In the case of methadone, 53 deaths (19%) occurred among people using diverted medication and 37% had an unknown treatment status. As the level of diversion is likely to be different between methadone and naltrexone, this

inflates the mortality rate associated with methadone treatment.

Conclusions

Deaths related to both antagonist and agonist pharmacotherapy for opioid dependence can and do occur. Naltrexone treatment shows a higher mortality risk in comparison to both agonist pharmacotherapies and active-dependent heroin use. This is especially concerning, considering that the majority of opioid-dependent individuals will return to opioid use soon after leaving naltrexone treatment. This high mortality rate should be emphasised to patients and considered by medical practitioners when determining a patient's suitability for naltrexone treatment. It is recommended that future trials of opioid dependence treatments include monitoring of post-treatment mortality risk for up to 12 months. Better systems to identify naltrexone-related death would be helpful, especially those that capture deaths occurring soon after treatment cessation.

Acknowledgements

Both authors are funded by the Australian Government Department of Health and Ageing and received a small additional grant to fund this study. Ethics approval was granted by both the University of New South Wales Human Research Ethics Committee and Monash University National Centre for Coronial Information. Thanks go to Stuart Gilmour, who assisted with data analysis.

References

[1] Oppenheimer E, Tobutt C, Taylor C, *et al.* Death and survival in a cohort of heroin addicts from London clinics: a 22-year follow-up study. Addiction 1994;89:1299–308.

[2] Hser YI, Hoffman V, Grella CE, *et al.* A 33-year follow-up of narcotics addicts. Arch Gen Psychiatry 2001;58: 503–8.

[3] Degenhardt L, Hall W, Lynskey M, *et al.* Illicit drug use. In: Ezzati M, Lopez AD, Rodgers A, Murray R, eds. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Chapter 13. Geneva: World Health Organization, 2004:1109–76.

[4] Goldstein A, Herrera J. Heroin addicts and methadone treatment in Albuquerque: a 22-year follow-up. Drug Alcohol Depend 1995;40:139–50.

[5] Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. Lancet 1999;353:221–6.

[6] Caplehorn JRM, Dalton MSYN, Halder F, *et al.* Methadone maintenance and addicts' risk of fatal heroin overdose. Subst Use Misuse 1996;31:177–96.

[7] Mattick RP, Breen C, Kimber J, *et al.* Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2003:Issue 2.

[8] Davids E, Gastpar M. Buprenorphine in the treatment of opioid dependence. Eur Neuropsychopharmacol 2004;14: 209–16.

[9] Fiellin DA, Kleber H, Trumple-Hejduk JG, *et al.* Consensus statement on office-based treatment of opioid dependence using buprenorphine. J Subst Abuse Treat 2004;27:153–9.

[10] Mattick RP, Kimber J, Breen C, *et al.* Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 2003; Issue 2.

[11] Renault PF. Treatment of heroin-dependent persons with antagonists: current status. Report No. 28: NIDA Research Monograph no. 28. Maryland: National Institute on Drug Abuse, 1981.

[12] Tucker TK, Ritter AJ, Maher C, *et al.* Naltrexone maintenance for heroin dependence: uptake, attrition and retention. Drug Alcohol Rev 2004;23:299–309.

[13] Minozzi S, Amato L, Vecchi S, *et al.* Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev 2006;Issue 1.

[14] Frischer M, ed. Estimating the prevalence of drug abuse using the mortality multiplier method: an overview. Luxembourg: Office for Official Publications of the European Communities, 1998.

[15] Frischer M, Hickman M, Kraus L, *et al.* A comparison of different methods for estimating the prevalence of problematic drug misuse in Great Britain. Addiction 2001;96: 1465–76.

[16] Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. Med J Aust 1999;170:104–9.

[17] Zador D, Sunjic S. Deaths in methadone maintenance treatment in New South Wales, Australia 1990–1995. Addiction 2000;95:77–84.

[18] Corkery JM, Schifano F, Ghodse AH, *et al.* The effects of methadone and its role in fatalities. Hum Psychopharmacol 2004;19:565–76.

[19] Milroy CM, Forrest ARW. Methadone deaths: a toxiciological analysis. J Clin Pathol 2000;53:277–81.

[20] Walsh SL, Preston KL, Stitzer ML, *et al.* Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther 1994;55:569–80.

[21] Mattick RP, Digiusto E, Doran CM, *et al.* National evaluation of pharmacotherapies for opioid dependence: report of results and recommendations. Sydney: National Drug and Alcohol Research Centre, 2004.

[22] Lintzeris N, Clark N, Muhleisen P, *et al.* National clinical guidelines and procedures for the use of buprenorphine in the treatment of heroin dependence. Canberra: Department of Health and Aged Care, 2001.

[23] Schifano F, Corkery J, Gilvarry E, *et al.* Buprenorphine mortality, seizures and prescription data in the UK, 1980–2002. Hum Psychopharmacol 2005;20:343–8.

[24] Auriacombe M, Fatseas M, Dubernet J, *et al.* French field experience with buprenorphine. Am J Addict 2004; 13(Suppl 1):S17–28.

[25] Auriacombe M, Franques P, Tignol J. Deaths attributable to methadone vs. buprenorphine in France. JAMA 2001;285:3.

[26] Reisine T, Pasternak G. Opioid analgesics and antagonists. In: Hardman JG, Limbird LE, eds. Goodman & Gilman's The pharmacological basis of therapeutics, 9th edn. Sydney: McGraw-Hill, 1996.

[27] Bell J, Kimber J, Lintzeris N, *et al.* Clinical guidelines and procedures for the use of naltrexone in the management of opioid dependence. Canberra: Australian Government Department of Health and Ageing, 2003.

[28] Hamilton R, Olmedo R, Shah S, *et al*. Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. Acad Emerg Med 2002;9:63–8.
[29] Digiusto E, Shakeshaft A, Ritter A, *et al*. Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). Addiction 2004;99:450–60.
[30] Ritter AJ. Naltrexone in the treatment of heroin dependence: relationship with depression and risk of overdose. Aust NZ J Psychiatry 2002;36:224–8.
[31] Barker B, Conroy E, Degenhardt L, *et al*. Global indicators for monitoring the illicit drug environment of NSW. Sydney: National Drug and Alcohol Research Centre, University of New South Wales, 2004.
[32] Gibson A, Degenhardt L. Mortality related to naltrexone in the treatment of opioid dependence: a comparative analysis. Sydney: National Drug and Alcohol Research Centre, 2005.
[33] Bird SM, Hutchinson SJ. Male drugs-related deaths in the fortnight after release from prison: Scotland, 1996–99. Addiction 2003;98:185–90.
[34] Miotto K, McCann MJ, Rawson RA, *et al*. Overdose, suicide attempts and death among a cohort of naltrexone-treated opioid addicts. Drug Alcohol Depend 1997;45:131–4.
[35] Foy A, Sadler C, Taylor A. An open trial of naltrexone for opiate dependence. Drug Alcohol Rev 1998;17:167–74.
[36] Bell JR, Young MR, Masterman SC, *et al*. A pilot study of naltrexone-accelerated detoxification in opioid dependence. Med J Aust 1999;171:26–30.
[37] Hall W, Wodak A. Is naltrexone a cure for heroin dependence? The evidence so far is not promising. Med J Aust 1999;171:9–10.
[38] Ling W, Wesson DR. Naltrexone treatment for addicted health-care professionals: a collaborative private practice experience. J Clin Psychiatry 1984;45:46–8.
[39] Hulse GK, O'Neil G, Hatton M, *et al*. Use of oral and implantable naltrexone in the management of the opioid impaired physician. Anaesth Intens Care 2003;31:196–201.
[40] Foster J, Brewer C, Steele T. Naltrexone implants can completely prevent early (1- month) relapse after opiate detoxification: a pilot study of two cohorts totalling 101 patients with a note on naltrexone blood levels. Addict Biol 2003;8:211–17.
[41] Brewer C. Naltrexone implants for opiate addiction: new life for a middle-aged drug. Pharm J 2001;267:260.
[42] Comer SD, Collins ED, Kleber HD, *et al*. Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. Psychopharmacology 2002;159:351–60.
[43] Carreno JE, Alvarez CE, San Narciso GI, *et al*. Maintenance treatment with depot opioid antagonists in subcutaneous implants: an alternative in the treatment of opioid dependence. Addict Biol 2003;8:429–38.
[44] Hulse GK, Tait RJ. A pilot study to assess the impact of naltrexone implant on accidental opiate overdose in 'high-risk' adolescent heroin users. Addict Biol 2003;8:337–42.
[45] Oliver P. Fatal opiate overdose following regimen changes in naltrexone treatment. Addiction 2005;100:560–3.
[46] Arnold-Reed DE, Hulse GK, Hansson RC, *et al*. Blood morphine levels in naltrexone-exposed compared to non-naltrexone-exposed fatal heroin overdoses. Addict Biol 2003;8:343–50.
[47] Gossop M, Marsden J, Stewart D. Dual dependence: assessment of dependence upon alcohol and illicit drugs, and the relationship of alcohol dependence among drug misusers to patterns of drinking, illicit drug use and health problems. Addiction 2002;97:169–78.
[48] Buster MC, van Brussel GH, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction 2002;97:993–1001.