

Literature Review: Opioids and Death

compiled by Bill Stockdale (bstockale@msn.com)

This review is the result of searches for the terms opioid/opioid-related-disorders and death/ADE done in the PubMed database. This bibliography includes selected articles from the 1,075 found by searching during May, 2008, which represent key findings in the study of opioids. Articles for which there is no abstract are excluded. Also case reports and initial clinical trial reports are excluded. This is a compendium of all articles and do not lead to a specific target.

There are three major topics developed in the literature as shown in this table of contents;

- Topic One: Opioids in Causal Path to Death (page 1)
 - Prescription Drug Deaths (page 1)
 - Illicit Drug Deaths (page 30)
 - Neonatal Deaths (page 49)
- Topic Two: Deaths in Palliative Care and Pain Treatment (page 57)
- Topic Three: Pharmacology, Psychology, Origins of Abuse Relating to Death (page 72)
- Bibliography (page 77)

The three topics are presented below; each is followed in chronological order.

Topic One: Opioids in Causal Path to Death

Prescription Drug Deaths

Karlson et al. describe differences in treatment of acute myocardial infarction, including different opioid use among men and women. The question whether women and men with acute myocardial infarction (AMI) are treated differently is currently debated. In this analysis we compared pharmacological treatments and revascularization procedures during hospitalization and during 1 year of follow-up in 300 women and 621 men who suffered an AMI in 1986 or 1987 at our hospital. During hospitalization, the mean dose of morphine (+/- SD) during the first 3 days was higher in men compared to women (14.5 +/- 15.7 vs. 9.8 +/- 10.3 mg, $p < 0.001$), more men than women were given morphine after the first 24 h (65.4 vs. 49.0%, $p < 0.01$), and more men were prescribed anticoagulants at discharge (18 vs. 12%, $p < 0.05$). After 1 year more women than men were on diuretics (61.3 vs. 42.8%, $p < 0.001$) and a similar observation was made at discharge. This study was performed before thrombolytic therapy was routinely used.

The frequency of revascularization procedures did not differ between men and women during hospitalization or during the year of follow-up. In conclusion, **no major treatment differences, which could affect the prognosis, were found between women and men hospitalized due to AMI** in this study in the prethrombolytic era.[1]

In 1995, La Harpe and Fryc provide descriptive information about deaths of persons on methadone treatment. In Geneva **41 deaths associated with methadone have been observed between 1987 and 1993. In 11 cases death was caused by heroin overdose in combination with methadone. In 6 other cases (natural death, hanging, murder, road accident, drowning and burning) methadone, although in feeble doses, could have played a role in the circumstances leading to death. In 24 other cases, where methadone was the sole cause of death, 10 of these were in individuals participating in Methadone Maintenance Schemes**, but none in the first two weeks of the scheme, 8 occurred in the year following release from prison (3 less than two weeks after release), 11 were associated with a parallel intake of benzodiazepines and 8 with an intake of alcohol.[2]

Also in 1995, Ott et al. report counts of deaths in hospitals related to opioid use. The study describes consumption of and poisoning by analgesic drugs in Denmark during the period **1979-1992. During this period, fatal poisonings from analgesics almost doubled to 200 deaths per year (40% of all drug related deaths in Denmark)**. The annual consumption of opioids increased at the beginning of the period, but during 1985-1992 it was relatively constant at 20 million defined daily doses (DDD) and associated with 600 hospital admissions and 150-170 deaths due to poisoning per year. Within the opioid group dextropropoxyphene consumption and poisonings decreased following a National Board of Health initiative in 1985-1987. As for the weak analgesics, consisting mainly of paracetamol or salicylates, the total consumption increased gradually and reached 145 million DDD in 1992, corresponding to 160 tablets per inhabitant per year. This consumption was associated with approximately 750 hospital admissions and 40 deaths due to poisoning. As judged from the mortality per dose the weak analgesics are 20-30 times safer than the opioids.[3]

In 1996, Caplehorn et al. studied the rates of death for persons on methadone treatment. An admission cohort of 296 Australian methadone maintenance patients was followed over 15 years. The relative risks of death in and out of maintenance were calculated for two age groups, 20-29 and 30-39 years. **Heroin addicts in both age groups were one-quarter as likely to die while receiving methadone maintenance as addicts not in treatment.** This is because they were significantly less likely to die by heroin overdose or suicide while in maintenance. Methadone maintenance had no measurable effect on the risk of death through non-heroin overdose, violence or trauma, or natural causes. A meta-analysis showed the reduction in overall mortality was consistent with the results of cohort studies conducted in the United States, Sweden, and Germany. **The combined results of the five studies again indicated that methadone maintenance reduced addicts' risk of death to a quarter, RR 0.25 (95% CI 0.19 to 0.33).**[4]

Reynaud et al., in 1998, report on deaths of drugs used to treat addiction. AIMS: Buprenorphine at high dosage became available in 1996 for substitution treatment in France. This drug is considered particularly safe and has become widely available in general medical practice. We investigated the possible implication of a buprenorphine-benzodiazepine association in six deaths of known abusers. DESIGN: Full investigation of cause of death was conducted for six drug abusers. SETTING: The deaths occurred in two regions of France (Auvergne and Lorraine). Assays were carried out by the Institut de Medecine Legale at Strasbourg, France, one of the few French laboratories equipped to assay buprenorphine. MEASUREMENT: First, the blood and urine underwent triple exhaustive screening. Secondly, buprenorphine and norbuprenorphine were analysed in all the autopsy samples by HPLC/MS. FINDINGS: **Benzodiazepine-buprenorphine associations were found in every case; no other substances that could account for the death were found.** The tissue concentrations were markedly higher than the blood levels. CONCLUSION: If the number of deaths linked to such drug misuse proves high, it may be necessary to review how buprenorphine is dispensed.[5]

Also in 1998, Tracqui et al report deaths from buprenorphine. OBJECTIVES: Buprenorphine has been an important advance in care for drug abusers, but the toxic risk

may be fatal. We report here two original series of buprenorphine **poisoning** in opiate abusers on substitution therapy. **PATIENTS:** The first series included 20 males and 9 females, aged 20-35 years (mean = 27.5) with non-fatal poisoning. The second series included 20 subjects (19 males, 1 female) aged 14-48 years (mean = 26.6) with a fatal outcome. All subjects were opiate addicts taking high-dosage sublingual buprenorphine formulation as substitution therapy. **RESULTS: Blood concentrations of buprenorphine were found in all cases to remain at a low level (1.0-2.3 ng/ml, m = 1.4 ng/ml, and 1.1-29.0 ng/ml, m = 8.4 ng/ml in non-fatal and fatal cases respectively). Almost all cases involved concomitant intake of psychotropic medications, especially benzodiazepines (18 non-fatal and 17 fatal cases).** **DISCUSSION:** These observations confirm previously reported data on the danger of buprenorphine-benzodiazepine combinations. Intravenous injection of crushed tablets also appears to be a risk factor (8 deaths and 10 non-fatal poisonings). This series highlights the need for improvement in the recently developed French program for substitution therapy with high-dosage buprenorphine in heroin addicts.[6]

Madadi et al. report on the effects of codeine used by breast feeding mothers. **QUESTION:** Recently a newborn died from morphine poisoning when his mother used codeine while breastfeeding. Many patients receive codeine for postlabour pain. Is it safe to prescribe codeine for nursing mothers? **ANSWER:** When a mother is an ultrarapid metabolizer of cytochrome P450 2D6, she produces much more morphine when taking codeine than most people do. In this situation, **newborns might be exposed to toxic levels of morphine when breastfeeding.** Options to reduce this risk include discontinuing codeine after 2 to 3 days of use and being aware of symptoms of potential opioid toxicity in both mothers and newborns.[7]

In 1998, Fohr suggests a double effect of using opioids. **The principle of double effect is used to justify the administration of medication to relieve pain even though it may lead to the unintended, although foreseen, consequence of hastening death by causing respiratory depression.** Although a review of the medical literature reveals that the risk of respiratory depression from opioid analgesic is more myth than fact and that there is little evidence that the use of medication to control pain hastens death, the belief

in the double effect of pain medication remains widespread. Applying the principle of double effect to end-of-life issues perpetuates this myth and results in the undertreatment of physical suffering at the end of life. The concept of double effect of opioids also has been used in support of legalization of physician-assisted suicide and euthanasia.[8]

Fields et al. studied opioid use in nursing homes. **BACKGROUND:** In a prospective study of nursing home residents, we found adverse drug events (ADEs) to be common, serious, and often preventable. To direct prevention efforts at high-risk residents, information is needed on resident-level risk factors. **METHODS:** Case-control study nested within a prospective study of ADEs among residents in 18 nursing homes. For each ADE, we randomly selected a control from the same home. Data were abstracted from medical records on functional status, medical conditions, and medication use. **RESULTS: Adverse drug events were identified in 410 nursing home residents.** Independent risk factors included being a new resident (odds ratio [OR], 2.8; 95% confidence interval [CI], 1.5-5.2) and taking anti-infective medications (OR, 4.0; CI, 2.5-6.2), antipsychotics (OR, 3.2; CI, 2.1-4.9), or antidepressants (OR, 1.5; CI, 1.1-2.3). The number of regularly scheduled medications was associated with increased risk of ADEs; the OR associated with taking 5 to 6 medications was 2.0 (CI, 1.2-3.2); 7 to 8 medications, 2.8 (CI, 1.7-4.7); and 9 or more, 3.3 (CI, 1.9-5.6). Taking supplements or nutrients was associated with lower risk (OR, 0.42; CI, 0.27-0.63). Preventable ADEs occurred in 226 residents. Independent risk factors included taking opioid medications (OR, 6.6; CI, 2.3-19.3), antipsychotics (OR, 4.0; CI, 2.2-7.3), anti-infectives (OR, 3.0; CI, 1.6-5.8), antiepileptics (OR, 2.2; CI, 1.1-4.5), or antidepressants (OR, 2.0; CI, 1.1-3.5). Scores of 5 or higher on the Charlson Comorbidity Index were associated with increased risk of ADEs (OR, 2.6; CI, 1.1-6.0). **The number of regularly scheduled medications was also a risk factor: the OR for 7 to 8 medications was 3.2 (CI, 1.4-6.9) and for 9 or more, 2.9 (CI, 1.3-6.8).** Residents taking nutrients or supplements were at lower risk (OR, 0.27; CI, 0.14-0.50). **CONCLUSIONS:** It is possible to identify nursing home residents at high risk of having an ADE. Particular attention should be directed at new residents, those with multiple medical conditions, those taking multiple medications, and those taking psychoactive medications, opioids, or anti-infective drugs.[9]

In 1997, Leander et al. described differences between deaths of persons on dextropropoxyphene [Darvocet] and other opioids. They studied deaths following intoxication with dextropropoxyphene (D) and opioids (M) in Denmark 1979-1992 with special reference to the sex, age group, contributory cause of death (secondary diagnosis) and manner of death. Deaths following D increased until 1985 for both sexes, where a total of 46 women and 64 men died. In 1985 the National Board of Health drew public attention to this problem which led to a decrease in these deaths among men, while in women a paradoxical increase in suicides outnumbered a reduction in deaths from intoxication accidents. In 1988 D was assigned to the more restrictive prescription rules of opioids, which further reduced the number of deaths. **The reduction of dextropropoxyphene deaths was followed by a corresponding increase in deaths due to opioids.** However, the demographic characteristics of D and M deaths were not entirely identical: The typical D victim had a history of psychiatric disease or drug/alcohol abuse and committed suicide; the age was 40-59 for women and 20-39 for men. The typical M victim also had a history of psychiatric disease and substance abuse but suicides were less common and the majority occurred in the age group 20-39 in both sexes. Both D and M deaths were rare in persons with a somatic secondary diagnosis. We conclude that these poisonings warrant continued attention, and that a more restrictive prescription practice of D and M to patients at risk is justified.[10]

In 1999, D'Eramo studied the **mortality of anesthetics used by dentists.**
PURPOSE: This study documented the incidence of mortality and morbidity for outpatient anesthesia delivered by oral and maxillofacial surgeons in Massachusetts.
MATERIALS AND METHODS: A questionnaire was mailed to the 151 active members of the Massachusetts Society of Oral and Maxillofacial Surgeons, and all members responded. Information regarding the incidence of specific anesthetic morbidity was reported for 1 year (1994), and the incidence of mortality for 5 years (1990 to 1994) was requested. RESULTS: Approximately 1,500,000 patients underwent office treatment in the 5-year period without an office anesthetic death. The most common complication was syncope occurring in 1 of every 142 patients receiving local anesthesia. In patients undergoing general anesthesia, laryngospasm occurred 10 times more frequently than bronchospasm. The incidence of other specific anesthetic complications are documented.

CONCLUSION: The results of this study suggest that the **incidence of death associated with office anesthesia, although small initially, has decreased.**[11]

Jonnason et al. report on deaths comparing Darvocet and other drugs. In Sweden, the frequency of fatal poisoning by dextropropoxyphene (DXP) ingestion is constantly high. There are seven preparations containing DXP on the Swedish market; in three of them DXP is the sole analgesic ingredient, while four of them are combinations of analgesics. In an attempt to assess the death rate attributable to each DXP preparation on the basis of toxicological analyses, altogether 834 cases of dextropropoxyphene-related death over a 5-year period (1992-1996) in Sweden have been reviewed. The ratio between number of fatal poisonings and prescription of defined daily dose/1000 inhabitants during a 12-month period (DDD) was determined. The highest ratio, 27, was attributed to unmixed preparations. The ratio for DXP + paracetamol-related deaths was 6.3, and for DXP + phenazone, 6.4, while the lowest ratio, 2, was found among the DXP + chlorzoxazone cases. The unmixed preparations, representing 26% of all DXP prescriptions during the study years, were implicated in 62% of the DXP fatalities, a considerable over-representation. Unmixed preparations, with their higher content of DXP, may be more attractive for many consumers because of their narcotic (euphoric) effects rather than for any analgetic superiority. Another possibility is that unmixed preparations may erroneously have been regarded as safer than when combined with paracetamol, as reports of poisoning with compounds containing DXP + paracetamol have been most frequently reported, probably due to their predominance on the market.[12]

In 2000, Karch and Stephens **suggest that the existence of methadone in a corpse is indicative of that drug as a cause of death.** **OBJECTIVES:** To clarify the mechanisms and risk factors of methadone toxicity and to describe the findings of deaths related to methadone use Design Retrospective review of case notes in the records of the San Francisco Medical Examiner comparing the findings in cases where methadone was deemed the cause of death with findings in decedents where methadone was an incidental finding, and with 50 age-matched, disease and drug free, trauma victims. **RESULTS:** 38 cases out of the 3317 processed by our office during 1997-1998 were identified in which

methadone had been detected. Cases were mostly male 28/38 (74%) and white, 28/38 (74%). In 17 of 38 cases death was deemed to have been caused by methadone toxicity. For the group the mean blood methadone concentration for all 38 patients, was 957 ng/ml SD = .681, SE = .14). The mean blood concentration of the main methadone metabolite (EDDP) was 253 ng/ml, SD = 529 ng/ml, SE = .089. The mean ratio of methadone in the blood to EDDP in the blood was 13.6:1 Values were not significantly different between cases in which methadone toxicity was the cause of death and in those in which it was an incidental finding. Cocaine, or the cocaine metabolite benzoylecgonine, was detected in the blood or urine of 16/38 cases (42%); morphine in one-third (13/38) and methamphetamine in only one. Pulmonary edema was evident in all cases, coronary artery disease in 9/38 (24%) and cirrhosis in 7/38 (18%) of the methadone users. Necrotizing fasciitis was the cause of death in 4 of the 38 methadone users (11%). Nationally, a sizeable percent of methadone deaths are from drugs diverted from treatment programs. **CONCLUSIONS: The presence of methadone is often an incidental finding during postmortem examination which is unrelated to the cause of death. Postmortem measurements of methadone or its metabolite, or both, cannot be used in isolation to identify which deaths are associated with methadone toxicity.**[13]

In 2003, Oderda et al. reported on opioid use in surgical patients. Opioids have demonstrated efficacy and often are drugs of choice in the management of postoperative pain. However, their use is often limited by adverse drug events (ADEs). The objective of this study was to determine the ADE rate in adult surgical patients who received opioids and the impact of opioid ADEs on length of stay (LOS), costs, and mortality. A hospital-based computerized system detected potential ADEs. Adult patients were selected if they received at least one dose of opioid medication during a surgical hospitalization between 1 January 1990 and 31 December 1999. Control patients were matched based on matching length of stay ([LOS] at least as long as time to ADE), age (within 10 years), sex, admission year, major disease category (MDC), and without an ADE. Linear regression models were used to determine the predictors of increased LOS, total hospital costs, and log-transformed total hospital costs. **60,722 patients received opioid medication during their surgical hospitalization and 2.7% experienced an opioid-**

related ADE. The most common clinical manifestations were nausea and vomiting (67%), and rash, hives, or itching (33.5%). No statistically significant difference was seen in mortality between ADE/non-ADE patients. ADE patients had statistically significant increases in LOS (0.53 days) and in log-transformed cost (16%). The estimated log cost difference of 16%, if applied to the median cost patient in the non-ADE group, averaged US\$ 840. Opioid-related ADEs are common in hospitalized patients and increase LOS and total hospital costs.[14]

Strang et al, in 1999, suggest preventions for naloxone overdoses. AIMS: Before proceeding with the introduction of an overdose fatality prevention programme including teaching in cardio-pulmonary resuscitation and distribution of naloxone, a pre-launch study of treatment and community samples of injecting drug misusers has been undertaken to establish (i) the extent of witnessing overdoses, (ii) the acceptability of naloxone distribution and training; and (iii) the likely impact of such measures. DESIGN AND SETTING: Structured interview of two samples: (a) a community sample of injecting drug misusers recruited by selected privileged access interviewers (PAI) and interviewed by them in community settings and (b) a treatment sample of opiate addicts recruited from our methadone maintenance clinic (interviewed by in-house research staff). PARTICIPANTS: (a) Three hundred and twelve injecting drug misusers with a history of having injected and currently still using injectable drugs; and (b) 142 opiate addicts in treatment at our local catchment area methadone maintenance clinic in South London. FINDINGS: **History of personal overdose was found with 38% of the community sample and 55% of the treatment sample--mainly involving opiates and in the company of friends. Most (54% and 92%, respectively) had witnessed at least one overdose (again mostly involving opiates), of whom a third had witnessed a fatal overdose. Only a few (35%) already knew of the existence and effects of naloxone. After explanation to the treatment sample, 70% considered naloxone distribution to be a good proposal.** Of the 13% opposed to the proposal, half thought it may lead them to use more drugs. Eighty-nine per cent of those who had witnessed an overdose fatality would have administered naloxone if it had been available. We estimate that at least two-thirds of witnessed overdose fatalities could be prevented by administration of home-based supplies of naloxone. CONCLUSIONS: Substantial proportions of both

community and treatment samples of drug misusers have witnessed an overdose death which could have been prevented through prior training in resuscitation techniques and administration of home-based supplies of naloxone. Such a new approach would be supported by most drug misusers. On the basis of these findings, we conclude that it is appropriate to proceed to a carefully constructed trial of naloxone distribution.[15]

Vilke et al. **did not find a link between overdose and naloxene.** OBJECTIVE: Naloxone is frequently used by prehospital care providers to treat suspected heroin and opioid overdoses. The authors' EMS system has operated a policy of allowing these patients, once successfully treated, to sign out against medical advice (AMA) in the field. This study was performed to evaluate the safety of this practice. METHODS: The authors retrospectively reviewed all 1996 San Diego County Medical Examiner's (ME's) cases in which opioid overdoses contributed to the cause of death. The records of all patients who were found dead in public or private residences or died in emergency departments of reasons other than natural causes or progression of disease, are forwarded to the ME office. ME cases associated with opiate use as a cause of death were cross-compared with all patients who received naloxone by field paramedics and then refused transport. The charts were reviewed by dates, times, age, sex, location, and, when available, ethnicity. RESULTS: There were 117 ME cases of opiate overdose deaths and 317 prehospital patients who received naloxone and refused further treatment. When compared by age, time, date, sex, location, and ethnicity, there was no case in which a patient was treated by paramedics with naloxone within 12 hours of being found dead of an opiate overdose. CONCLUSIONS: Giving naloxone to heroin overdoses in the field and then allowing the patients to sign out AMA resulted in no death in the one-year period studied. This study did not evaluate for return visits by paramedics nor whether patients were later taken to hospitals by private vehicles.[16]

In 2002, Kintz et al. describe deaths related to the use of Buprenorphine. OBJECTIVES: Buprenorphine at high dosage became available in France in 1996, as a substitution treatment for heroin addicts. Since this date, numerous deaths were attributed to this drug. This paper reports a new series of 13 fatalities involving buprenorphine observed at the Institute of Legal Medicine of Strasbourg, between August 2000 to

October 2001. DESIGN AND METHODS: During the mentioned period, about 800 forensic cases were screened at the laboratory. Buprenorphine and its primary metabolite norbuprenorphine were assayed in postmortem specimens by HPLC/MS. From these 13 subjects, 11 were male. Blood levels ranged from 0.3 to 7.7 ng/mL (mean 3.5 ng/mL) and 0.3 to 16.2 ng/mL (mean 2.9 ng/mL) for buprenorphine and norbuprenorphine, respectively. The mean values appear to be within the therapeutic range.

CONCLUSIONS: IV injection of crushed tablets, a concomitant intake of psychotropics (especially benzodiazepines and neuroleptics) and the high dosage of the buprenorphine formulation available in France appear as the major risk factors for such fatalities.[17]

Adverse effects of self regulated opioid use were reported by Hankin et al. in 2007. PURPOSE: This article systematically characterizes aspects of all Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) reports associated with i.v. patient-controlled analgesia (PCA) postoperative use during a two-year index period. METHODS: Intravenous PCA represents a well-accepted and satisfactory means of acute pain treatment; case reports and large case series have described the occurrence of i.v. PCA-related adverse drug events (ADEs). MAUDE data files were downloaded, and all records pertaining to i.v. PCA devices were extracted for the two-year period from January 1, 2002, through December 31, 2003. Medical device events were categorized by their reported cause, including patient-related event, device safety event, operator error, and adverse reactions to opioids. Because there was not sufficient information to grade the certainty of each reported cause, all reported causes were graded "possible," except for device safety events that were confirmed on inspection by the manufacturer. RESULTS: **There were 2009 individual i.v. PCA-related MAUDE medical device events reported during the two-year period. Of these events, 1590 (79.1%) were classified as possible device safety events, 131 (6.5%) as possible operator error, 25 (1.2%) as possible adverse reactions to opioids, 12 (0.6%) as possible patient-related events, and 235 (11.7%) as indeterminate.** CONCLUSION: Manufacturer-confirmed device malfunction was a major cause of reported ADE with i.v. PCA infusion pumps while operator errors were more likely to be associated with more serious adverse outcomes than device safety problems. To reduce

the incidence of these problems, potential vulnerabilities in the design and manufacture of i.v. PCA pumps must be identified and addressed.[18]

In 2004, Digiusto et al. reported on adverse events during treatment for opioid dependence. AIMS: The study estimated serious adverse event (SAE) rates among entrants to pharmacotherapies for opioid dependence, during treatment and after leaving treatment. DESIGN: A longitudinal study based on data from 12 trials included in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD). PARTICIPANTS AND SETTINGS: A total of 1244 heroin users and methadone patients treated in hospital, community and GP settings. Intervention Six trials included detoxification; all included treatment with methadone, buprenorphine, levo-alpha-acetyl-methadol (LAAM) or naltrexone. FINDINGS: During 394 person-years of observation, 79 SAEs of 28 types were recorded. Naltrexone participants experienced 39 overdoses per 100 person-years after leaving treatment (44% occurred within 2 weeks after stopping naltrexone). This was eight times the rate recorded among participants who left agonist treatment. Rates of all other SAEs were similar during treatment versus out of treatment, for both naltrexone-treated and agonist-treated participants. Five deaths occurred, all among participants who had left treatment, at a rate of six per 100 person-years. Total SAE rates during naltrexone and agonist treatments were similar (20, 14 per 100 person-years, respectively). Total SAE and death rates observed among participants who had left treatment were three and 19 times the corresponding rates during treatment. CONCLUSIONS: **Individuals who leave pharmacotherapies for opioid dependence experience higher overdose and death rates compared with those in treatment.** This may be due partly to a participant self-selection effect rather than entirely to pharmacotherapy being protective. Clinicians should alert naltrexone treatment patients in particular about heroin overdose risks. Duty of care may extend beyond cessation of dosing.[19]

In 2005, Franklin et al. reported on deaths related to dosing trends. BACKGROUND: **The use of opioids for chronic non-cancer pain has increased in the United States since state laws were relaxed in the late 1990s.** These policy changes occurred despite scanty scientific evidence that chronic use of opioids was safe and

effective. METHODS: We examined opiate prescriptions and dosing patterns (from computerized databases, 1996 to 2002), and accidental poisoning deaths attributable to opioid use (from death certificates, 1995 to 2002), in the Washington State workers' compensation system. RESULTS: Opioid prescriptions increased only modestly between 1996 and 2002. **However, prescriptions for the most potent opioids (Schedule II), as a percentage of all scheduled opioid prescriptions (II, III, and IV), increased from 19.3% in 1996 to 37.2% in 2002. Among long-acting opioids, the average daily morphine equivalent dose increased by 50%, to 132 mg/day. Thirty-two deaths were definitely or probably related to accidental overdose of opioids.** The majority of deaths involved men (84%) and smokers (69%). CONCLUSIONS: The reasons for escalating doses of the most potent opioids are unknown, but it is possible that tolerance or opioid-induced abnormal pain sensitivity may be occurring in some workers who use opioids for chronic pain. Opioid-related deaths in this population may be preventable through use of prudent guidelines regarding opioid use for chronic pain.[20]

Gillman is published in 2005 with a report of life threatening toxicity of opioids used in conjunction with other drugs. Toxicity resulting from excessive intra-synaptic serotonin, historically referred to as serotonin syndrome, is now understood to be an intra-synaptic serotonin concentration-related phenomenon. Recent research more clearly delineates serotonin toxicity as a discreet toxidrome characterized by clonus, hyper-reflexia, hyperthermia and agitation. Serotonergic side-effects occur with serotonergic drugs, and overdoses of serotonin re-uptake inhibitors (SRIs) frequently produce marked serotonergic side-effects, and in 15% of cases, moderate serotonergic toxicity, but not to a severe degree, which produces hyperthermia and risk of death. **It is only combinations of serotonergic drugs acting by different mechanisms that are capable of raising intra-synaptic serotonin to a level that is life threatening.** The combination that most commonly does this is a monoamine oxidase inhibitor (MAOI) drug combined with any SRI. There are a number of lesser-known drugs that are MAOIs, such as linezolid and moclobemide; and some opioid analgesics have serotonergic activity. These properties when combined can precipitate life threatening serotonin toxicity. Possibly preventable deaths are still occurring. Knowledge of the properties of these drugs will therefore help to ensure that problems can be avoided in most clinical situations, and treated

appropriately (with 5-HT(2A) antagonists for severe cases) if they occur. The phenylpiperidine series opioids, pethidine (meperidine), tramadol, methadone and dextromethorphan and propoxyphene, appear to be weak serotonin re-uptake inhibitors and have all been involved in serotonin toxicity reactions with MAOIs (including some fatalities). Morphine, codeine, oxycodone and buprenorphine are known not to be SRIs, and do not precipitate serotonin toxicity with MAOIs.[21]

In 2005, Good et al. found no correlation between opioid dosage and survival in a palliative care environment. AIMS: To assess whether opioid and sedative medication use affects survival (from hospice admission to death) of patients in an Australian inpatient palliative care unit. BACKGROUND: Retrospective audit. Newcastle Mercy Hospice--a tertiary referral palliative care unit. All patients who died in the hospice between 1 February and 31 December 2000. METHODS: Length of survival from hospice admission to death, and the median and mean doses of opioids and sedatives used in the last 24 h of life. Comparison of these with published studies outside of Australia. RESULTS: In this study, the use of opioids, benzodiazepines and haloperidol did not have an association with shortened survival and the only statistical significant finding was an increased survival in patients who were on 300 mg/day or more of oral morphine equivalent (OME). The proportion of patients requiring greater than or equal to 300 mg OME/day (at 28%) was higher than published studies, but the mean dose of 371 mg OME/day was within the range of other studies. The proportion of patients receiving sedatives (94%) was higher than other studies, but the median dose of parenteral midazolam equivalent of 12.5 mg per 24 h was lower than other studies from outside Australia. CONCLUSIONS: **There was no association between the doses of opioids and sedatives on the last day of life and survival (from hospice admission to death) in this population of palliative care patients.**[22]

Maxwell et al., in 2005, studied deaths related to methadone treatment. **This study analyzes causes of deaths of 766 patients who died while in methadone treatment in Texas between 1994 and 2002. Compared with deaths in the general population of Texas, deaths of clients in methadone treatment were 4.6 times more likely to be from a drug overdose, 3.4 times more likely to be from liver disease, 1.7**

times more likely to be from a respiratory disease, 1.5 times more likely to be from a homicide and 1.4 times more likely to be from AIDS, but less likely to be from suicide, motor vehicle accidents, cardiovascular diseases or cancer. Of the clients, 20% died of liver disease, 18% of cardiovascular disease and 14% of drug overdose. An older cohort had been in treatment longer, had more take-homes, were on higher doses and tended to die of chronic diseases. A younger cohort tended to die from traumas, including drug overdose. Time in treatment was 43.3 months; mean daily dose was 77.3mg; number of days/month dosed in the clinic was 13.9. Given these rates, the scope of services should include on-site treatment for other medical conditions and staff should be educated about and counsel about the risk of death for new patients.[23]

Morgan et al. report on mortality rates of acetaminophen and compounds, including opioids, in England. **BACKGROUND:** About 500 drug poisoning deaths involving paracetamol (acetaminophen) occur every year in England and Wales. To reduce the number of deaths, regulations were introduced in 1998 to restrict the sale of paracetamol. In this paper, we evaluate the impact of these regulations. **METHODS:** Mortality data for England and Wales were provided by the Office for National Statistics. Deaths were defined as due to compound paracetamol (paracetamol in combination with another analgesic, a low dose opioid or other ingredients) or paracetamol only, with or without alcohol or other drugs. The Department of Health provided data on all hospital admissions with a primary diagnosis of paracetamol poisoning. **RESULTS:** Mortality rates for paracetamol only were similar for males and females, and decreased from about 4.5 to 2.8 per million between 1997 and 1999 and again from about 3.1 to 2.2 per million between 2001 and 2002. These falls may be attributable to random variation in the rates. Deaths involving compound paracetamol, which were not subject to the 1998 regulations, remained relatively constant over the study period. There was evidence of a decreasing trend in paracetamol only mortality rates and this followed overall trends for other drug poisoning excluding opioids and drugs of misuse. **Hospital admissions due to paracetamol poisoning increased from about 27 000 to 33 000 between 1995/1996 and 1997/1998 and then decreased to 25 000 in 2001/2002.** There were almost 50 per cent more admissions for females than males, with the highest admission rates amongst females aged 15-24 years old. **CONCLUSIONS:** Between 1993 and 2002, mortality rates

and hospital admissions due to paracetamol poisoning declined. However, the contribution of the 1998 regulations to this decline is not clear. Paracetamol poisoning continues to be an important public health issue in England and Wales and represents significant workload for the NHS in England.[24]

Rehm et al. report on mortality in a Swiss methadone program. **BACKGROUND:** A major goal of heroin-assisted treatment in Switzerland has been to reduce the drug-related mortality of heroin users. Therefore, a continuous monitoring of deaths under treatment is essential. **AIMS:** To assess mortality of participants in heroin-assisted treatment in Switzerland over a 7-year period from 1994 to 2000, and to compare this mortality to the general population and to other populations of opioid users, as reported in the literature. **METHOD:** Estimation of person years under heroin-assisted treatment from the complete case registry of heroin-assisted treatment in Switzerland. Estimation of standardized mortality ratios comparing the population in treatment to the Swiss population (standardized to the year 2000). **RESULTS: Over the 7-year period, the crude death rate of patients in heroin-assisted treatment, and including one month after discharge from treatment, was 1% per year. The standardized mortality ratio for the entire observation period was 9.7 (95% C.I. 7.3-12.8), with females having higher standardized mortality ratios (SMR 17.2) than males (SMR 8.4). There was no clear time trend.** **CONCLUSION:** Mortality in heroin-assisted treatment was low compared to the mortality rate of Swiss opioid users 1990s (estimated to be between 2.5 and 3%). It was also low compared to mortality rates of opioid users in other maintenance treatments in other countries as reported in the literature. The SMR was also lower than that reported in the only meta-analysis in the literature: 13.2 (95% C.I. 12.3-14.1). The low mortality rate is all the more noteworthy as heroin-assisted treatment in Switzerland included only refractory opioid addicts with existing severe somatic and/or mental problems.[25]

Wolf et al., in 2005, studied deaths involving oxycodone. Oxycodone is a potent semi-synthetic narcotic prescribed for the management of pain. Previous investigators have reported that the abuse of oxycodone is most frequently seen in conjunction with the abuse of other drugs, although fatalities have been reported with oxycodone alone. We

undertook a retrospective review of cases investigated by the Palm Beach County Medical Examiner's Office in which postmortem toxicologic studies indicated the presence of oxycodone. A total of 172 consecutive cases were studied, including 18 in which death was attributed to oxycodone toxicity, 117 to combined drug toxicity, 23 to trauma, 9 to natural causes and 5 to another drug or drugs. The postmortem blood concentrations of oxycodone overlapped among the groups. **The mean blood oxycodone concentration among the cases of oxycodone toxicity was 0.69 mg/L, combined drug toxicity 0.72 mg/L and trauma 0.62 mg/L. Concentrations were lower in cases of deaths attributed to natural causes and to another drug or drugs (mean each 0.087 mg/L).** Benzodiazepines, detected in 96 cases, were the most common co-intoxicants in the cases of combined drug toxicity, followed by cocaine, which was found in 41. The most frequently encountered benzodiazepine was alprazolam. **This study confirms that deaths in which oxycodone is a factor are most commonly cases of combined drug toxicity. The high incidence of alprazolam as a co-intoxicant has not been previously recognized.**[26]

In 2006, Bhananker et al. reported on **mortality related to use of anesthesia**. **BACKGROUND:** To assess the patterns of injury and liability associated with monitored anesthesia care (MAC) compared with general and regional anesthesia, the authors reviewed closed malpractice claims in the American Society of Anesthesiologists Closed Claims Database since 1990. **METHODS:** All surgical anesthesia claims associated with MAC (n = 121) were compared with those associated with general (n = 1,519) and regional (n = 312) anesthesia. A detailed analysis of MAC claims was performed to identify causative mechanisms and liability patterns. **RESULTS:** MAC claims involved older and sicker patients compared with general anesthesia claims (P < 0.025), often undergoing elective eye surgery (21%) or facial plastic surgery (26%). **More than 40% of claims associated with MAC involved death or permanent brain damage, similar to general anesthesia claims.** In contrast, the proportion of regional anesthesia claims with death or permanent brain damage was less (P < 0.01). Respiratory depression, after absolute or relative overdose of sedative or opioid drugs, was the most common (21%, n = 25) specific damaging mechanism in MAC claims. Nearly half of these claims were judged as preventable by better monitoring, including capnography, improved vigilance,

or audible alarms. On-the-patient operating room fires, from the use of electrocautery, in the presence of supplemental oxygen during facial surgery, resulted in burn injuries in 20 MAC claims (17%). **CONCLUSION:** Oversedation leading to respiratory depression was an important mechanism of patient injuries during MAC. Appropriate use of monitoring, vigilance, and early resuscitation could have prevented many of these injuries. Awareness and avoidance of the fire triad (oxidizer, fuel, and ignition source) is essential to prevent on-the-patient fires.[27]

In 2006, Chinnetto et al. describe **opioid prescriptions, including death outcome**. We evaluated patterns of use of opioids in palliative care across one region in Italy by cross-referencing a cancer registry with unique patient identifiers, with prescription databases. **There were 90 803 patients in the registry, of whom 39 597 died during the study period. Only 8539 (21%) of these were prescribed opioids at the time of their death. Prescribed daily doses of oral morphine used (45 mg) and of buprenorphine (0.71 mg) were low compared with injected morphine (28.6 mg, equivalent to approximately 90 mg of oral morphine) and especially with doses of transdermal fentanyl (1.13 mg, equivalent to approximately 180 mg morphine).** The reasons for this acceptance of transdermal fentanyl and reluctance to use oral morphine are unclear, but it seems that more effort in educating healthcare professionals and patients about the use of morphine would be useful. The use of more detailed prescribing data such as prescribed or received daily doses can add to our understanding of headline prescribing data.[28]

Cobaugh and Krenzelok, in 2006, use **poison control center data** to study adverse drug reactions, including opioids. **PURPOSE:** The severity of hazards posed by medications implicated in poisoning in older adults was characterized. **METHODS:** Toxic Exposure Surveillance System (TESS) cases from 1993 through 2002 involving a single substance in patients age 60 years or older and coded as an adverse drug reaction (ADR) or therapeutic error were analyzed. Hazard factors were determined for each exposure reason by calculating the sum of the major effects and deaths for each substance category and subcategory and dividing this by the total number of exposures for the respective category or subcategory. **RESULTS:** Hazard factors were calculated for

12,737 ADRs and 51,846 therapeutic errors. The overall rates of major effects and deaths were 7.5% and 1.6% in the ADR and therapeutic error groups, respectively. In the ADR group, five TESS categories had a hazard factor of $>$ or $=2.0$: anesthetics, anticoagulants, antineoplastics, cardiovascular drugs, and radiopharmaceuticals. In the therapeutic error group, five drug categories also had a hazard factor of $>$ or $=2.0$: anesthetics, anticoagulants, antineoplastics, asthma therapies, and serums/toxoids/vaccines. Six pharmaceutical categories were associated with hazard factors of $>$ or $=2.0$ in both the ADR and therapeutic error groups. **CONCLUSION: An analysis of ADRs and therapeutic errors involving older adults and reported to poison control centers from 1993 through 2002 revealed overall rates of major effects and death of 7.5% and 1.6% in the ADR and therapeutic error groups, respectively. Antineoplastics, aminophylline or theophylline, cardiac glycosides, heparin, morphine, and warfarin were implicated in more than 50 cases and associated with hazard factors of $>$ or $=2.0$ for both exposure groups.**[29]

In 2006, Martin et al. studied **fentanyl related deaths** in Canada. In order to characterize fentanyl-related deaths in the province of Ontario, Canada, a retrospective study of all cases in which fentanyl was quantitated in blood was conducted for the time period between 2002 and 2004. A total of 112 fentanyl-related deaths were identified. Decedents ranged in age from 4 to 93 years and comprised 63 men and 49 women. A variety of routes of administration of the drug were identified: transdermal application of Duragesic patches, intravenous injection of patch contents or fentanyl citrate solution, oral/transmucosal administration, and volatilization and inhalation of Duragesic systems. Blood fentanyl concentrations were determined for all modes of drug administration and are provided. **There were 54 cases in which death was attributed solely to fentanyl intoxication;** the mean blood concentration was 25 microg/L (range: 3.0-383 microg/L). This concentration range overlapped with blood fentanyl concentrations measured among cases where the presence of the drug was considered incidental. For example, a mean blood concentration of 12 microg/L was observed among 12 cases of natural death (range: 2.7-33 microg/L). Detailed case reports of six individuals are also included and provide additional insight into the use of this drug for both therapeutic and illicit means.[30]

Mueller et al., in 2006, studied overdose deaths from prescription drugs in New Mexico. **BACKGROUND: New Mexico has the highest rate of drug-induced mortality in the United States.** The contribution of prescription drugs to the total overdose death rate has not been adequately described. **METHODS:** A total of 1,906 unintentional drug overdose deaths occurring in 1994 to 2003 in New Mexico were analyzed. Unintentional drug overdose death was defined as death caused by prescription, illicit, or a combination of drugs, as determined by a pathologist. Deaths were investigated annually by the medical examiner and data were analyzed in 2004-2005. Rates and trends of total and prescription drug overdose death were calculated, decedent characteristics were analyzed, and common drug combinations causing death were described. **RESULTS:** The rate of unintentional prescription drug overdose death increased by 179% (1.9 to 5.3/100,000) from 1994 to 2003. A high percentage of prescription drug overdose decedents were white non-Hispanic (63.2%) and female (43.9%). These decedents were older and less frequently had alcohol listed as an additional cause of death than decedents of other drug overdose categories. Of all deaths caused by prescription drug(s) (n =765), 590 (77.1%) were caused by opioid painkillers, 263 (34.4%) by tranquilizers, and 196 (25.6%) by antidepressants. **CONCLUSIONS: The rate of prescription drug overdose death in New Mexico increased significantly over the 10-year study period.** Comprehensive surveillance of drug overdose deaths is recommended to describe their occurrence in the context of both medical and diverted use of prescription drugs. Understanding decedent profiles and the potential risk factors for prescription drug overdose death is crucial for effective drug overdose prevention education among healthcare providers.[31]

Paulozzi et al., in 2006, report on increased deaths in US and hint at **diversion**. **PURPOSE:** Since 1990, numerous jurisdictions in the United States (US) have reported increases in drug poisoning mortality. During the same time period, the use of opioid analgesics has increased markedly as part of more aggressive pain management. This study documented a dramatic increase in poisoning mortality rates and compared it to sales of opioid analgesics nationwide. **METHODS:** Trend analysis of drug poisoning deaths using **underlying cause of death and multiple cause of death mortality data from the Centers for Disease Control and Prevention and opioid analgesic sales data**

from the US Drug Enforcement Administration. RESULTS: Unintentional drug poisoning mortality rates increased on average 5.3% per year from 1979 to 1990 and 18.1% per year from 1990 to 2002. The rapid increase during the 1990s reflects the rising number of deaths attributed to narcotics and unspecified drugs. Between 1999 and 2002, the number of opioid analgesic poisonings on death certificates increased 91.2%, while heroin and cocaine poisonings increased 12.4% and 22.8%, respectively. By 2002, opioid analgesic poisoning was listed in 5528 deaths-more than either heroin or cocaine. The increase in deaths generally matched the increase in sales for each type of opioid. The increase in deaths involving methadone tracked the increase in methadone used as an analgesic rather than methadone used in narcotics treatment programs. **CONCLUSIONS:** A national epidemic of drug poisoning deaths began in the 1990s. Prescriptions for opioid analgesics also increased in this time frame and may have inadvertently contributed to the increases in drug poisoning deaths.[32]

In 2006, Lai et al. reported on deaths related to **Buprenorphine** in Singapore. Buprenorphine is available in Singapore as substitution treatment for opioid dependence since 2002. This study surveys buprenorphine related deaths in Singapore between September 2003 and December 2004. The aims are to establish the autopsy prevalence of buprenorphine related deaths and the demographical and toxicological profile of the cases. Toxicological screening was performed for all unnatural deaths, deaths involving known drug addicts, as well as when autopsy revealed no obvious cause of death. Twenty-one cases had buprenorphine detected in post-mortem blood and/or urine samples. Eighteen were sudden deaths. There were two fatal falls from height and one death by hanging. All subjects were male. The age range was 24-48 years. Fourteen subjects were between 30 and 39 years of age. The mean age was 35 years. The majority (62%) were Chinese. Eleven (52%) were known drug abusers. For sudden deaths, two groups were identified. Six cases died from natural causes. Blood buprenorphine levels ranged from undetected (detected in urine) to 3.2 ng/mL (mean 1.4 ng/mL). Twelve cases were attributed directly and indirectly to mixed drug poisoning. Blood buprenorphine levels ranged from undetected (detected in urine) to 17 ng/mL (mean 3.2 ng/mL). Nineteen cases showed concurrent abuse of buprenorphine and benzodiazepine, diazepam being the most frequently detected, followed by nitrazepam and midazolam. **The**

availability of buprenorphine as substitution therapy is associated with an increase in buprenorphine related deaths. The danger of co-abuse of buprenorphine and benzodiazepines is highlighted.[33]

Soyka et al., in 2006, studied mortality rates of substitution drugs. Mortality rates in drug-dependent patients in substitution treatment remain a matter of debate. Although several retrospective toxicological or forensic postmortem studies on this issue have been conducted, few prospective studies have addressed this problem. **In a nationally representative sample of 2694 opioid dependent patients in substitution treatment either with methadone or buprenorphine at baseline were monitored over a 12-month period (response rate, 91%). A total number of 1629 (60.4%) were still in treatment after 12 months. The overall mortality rate was 1.04%. In total, 28 patients of the initial sample deceased within the 1-year follow-up period. Eleven (0.4%) of these deaths are due to a fatal intoxication.** Three patients (0.1%) died of human immunodeficiency virus/acquired immunodeficiency syndrome, and 3 (0.1%) committed suicide. Thirteen of these patients (4 with overdose/polyintoxication) were not in substitution treatment at the time of death. Other reasons included accidents and deaths due to other medical conditions. Only in one case the reason could not be ascertained. The mortality rate was similar in methadone as compared with buprenorphine patients. Taking into account the high comorbidity of opioid dependent patients and the severity of dependence, the mortality rate of approximately 1% confirms that maintenance treatment could be regarded as a fairly safe treatment.[34]

In 2007, Oderda et al. (different from above 2003 study) studied costs and length of stay among surgical patients on prescribed opioids. **BACKGROUND:** Opioid analgesics remain a mainstay in the treatment of pain associated with surgical procedures. Such use is associated with adverse drug events (ADEs). **OBJECTIVE:** To investigate the impact of opioid-related ADEs on total hospital costs and length of stay (LOS) in adult surgical patients. **METHODS:** This was a retrospective matched cohort study using data from computerized medical records. ADE cases were prospectively detected using computerized surveillance and verified by pharmacists. Surgical patients treated at LDS Hospital in Salt Lake City from January 1, 1998, to December 31, 2003, were included.

The primary outcomes were costs and hospital LOS associated with opioid-related ADEs and the relationship of opioid dose to ADE events. RESULTS: **Patients experiencing opioid-related ADEs had significantly increased median total hospital costs (7.4% increase; 95% CI 3.83 to 10.96; p < 0.001) and increased median LOS (10.3% increase; 95% CI 6.5 to 14.2; p < 0.001) compared with matched non-ADE controls.** The increased costs attributable to ADEs, by surgery type, were general surgery (\$676.51; 95% CI 351.50 to 1001.50), orthopedics (\$861.50; 95% CI 448.20 to 1274.80), and obstetrics/gynecology (\$540.90; 95% CI 281.40 to 800.40). Similarly, increased LOS attributable to ADEs, by surgery type, were general surgery (0.64 days; 95% CI 0.40 to 0.88), orthopedics (0.52 days; 95% CI 0.33 to 0.71), and obstetrics/gynecology (0.53 days; 95% CI 0.33 to 0.72). Higher doses of opioids were associated with increased risk of experiencing ADEs (OR 1.3; 95% CI 1.07 to 1.60; p = 0.01). CONCLUSIONS: Opioid-related ADEs following surgery were associated with significantly increased LOS and hospitalization costs. These ADEs occurred more frequently in patients receiving higher doses of opioids.[35]

Davoli et al., in 2007, studied the mortality of **replacement and other therapies** for addicts. BACKGROUND: Specialist drug treatment is critical to overdose prevention; methadone maintenance is effective, but we lack evidence for other modalities. We evaluate the impact of a range of treatments for opiate dependence on overdose mortality. METHODS: Prospective cohort study of 10,454 heroin users entering treatment 1998-2001 in Italy followed-up for 10,208 person-years in treatment and 2,914 person-years out of treatment. Standardized overall mortality ratios (SMR) estimate excess mortality risk for heroin users in and out of treatment compared to the general population. Cox models compare the hazard ratio (HR) of overdose between heroin users in treatment and out of treatment. RESULTS: There were 41 overdose deaths, 10 during treatment and 31 out of treatment, **generating annual mortality rates of 0.1% and 1.1%** and SMRs of 3.9 [95% confidence interval (CI) 2.8-5.4] and 21.4 (16.7-27.4), respectively. Retention in any treatment was protective against overdose mortality (HR 0.09 95% CI 0.04-0.19) compared to the risk of mortality out of treatment, independent of treatment type and potential confounders. **The risk of a fatal overdose was 2.3% in the month immediately after treatment and 0.77% in the subsequent period; compared to the**

risk of overdose during treatment the HR was 26.6 (95% CI 11.6-61.1) in the month immediately following treatment and 7.3 (3.3-16.2) in the subsequent period.

CONCLUSIONS: We demonstrate that a range of treatments for heroin dependence reduces overdose mortality risk. However, the considerable excess mortality risk in the month following treatment indicates the need for greater health education of drug users and implementation of relapse and overdose death prevention programmes.[36]

Hartung et al. report adverse events of long acting opioids. **BACKGROUND:** Despite widespread use and emerging safety concerns, data on the **comparative safety and effectiveness of long-acting opioid (LAO) analgesics** are weak. **OBJECTIVE:** To compare rates of adverse events among patients newly prescribed an LAO. **METHODS:** A retrospective observational cohort study using Medicaid administrative claims data was conducted examining time until first adverse outcome among patients with new prescriptions for methadone, extended-release (ER) oxycodone, ER morphine, or transdermal fentanyl. Adverse outcomes included emergency department (ED) encounters or hospitalizations for opioid-related adverse events, all-cause ED encounters or hospitalizations, death, and diagnoses for opioid-related adverse effects. Cox proportional hazards models were used to adjust for a variety of measured covariates overall and within subgroups of patients with and without cancer. **RESULTS:** This study included 5684 subjects. Patients prescribed ER oxycodone were 55[corrected]% less likely (adjusted hazard ratio [HR] 0.45; 95% CI 0.26 to 0.77) to experience an ED or hospitalization involving an opioid-related adverse event, 23% lower risk of hospitalization (adjusted HR 0.77; 95% CI 0.66 to 0.91), 41% lower risk of constipation (adjusted HR 0.59; 95% CI 0.35 to 1.00), and a 29% lower risk of death (adjusted HR 0.71; 95% CI 0.54 to 0.94) compared with those prescribed ER morphine. Among subjects with noncancer pain, fentanyl was associated with a higher risk of ED encounters (adjusted HR 1.27; 95% CI 1.02 to 1.59) and methadone was associated with a greater risk of overdose symptoms (adjusted HR 1.57; 95% CI 1.03 to 2.40) compared with ER morphine. **CONCLUSIONS: Our results support a modest safety advantage with ER oxycodone compared with ER morphine. Among subjects with noncancer pain, fentanyl and methadone were associated with an increased risk of an adverse**

event compared with ER morphine. Additional studies are needed to confirm our findings and further clarify risks associated with different LAOs.[37]

In 2007, Hankin et al. report on adverse events associated with **intravenous analgesics**. **PURPOSE:** This article systematically characterizes aspects of all Food and Drug Administration Manufacturer and User Facility Device Experience (MAUDE) reports associated with i.v. patient-controlled analgesia (PCA) postoperative use during a two-year index period. **METHODS:** Intravenous PCA represents a well-accepted and satisfactory means of acute pain treatment; case reports and large case series have described the occurrence of i.v. PCA-related adverse drug events (ADEs). MAUDE data files were downloaded, and all records pertaining to i.v. PCA devices were extracted for the two-year period from January 1, 2002, through December 31, 2003. Medical device events were categorized by their reported cause, including patient-related event, device safety event, operator error, and adverse reactions to opioids. Because there was not sufficient information to grade the certainty of each reported cause, all reported causes were graded "possible," except for device safety events that were confirmed on inspection by the manufacturer. **RESULTS: There were 2009 individual i.v. PCA-related MAUDE medical device events reported during the two-year period. Of these events, 1590 (79.1%) were classified as possible device safety events, 131 (6.5%) as possible operator error, 25 (1.2%) as possible adverse reactions to opioids, 12 (0.6%) as possible patient-related events, and 235 (11.7%) as indeterminate.** **CONCLUSION:** Manufacturer-confirmed device malfunction was a major cause of reported ADE with i.v. PCA infusion pumps while operator errors were more likely to be associated with more serious adverse outcomes than device safety problems. To reduce the incidence of these problems, potential vulnerabilities in the design and manufacture of i.v. PCA pumps must be identified and addressed.[18]

Hull et al., in 2007, discuss results of mortalities associated with both licit and illicit fentanyl. Fatalities associated with fentanyl hydrochloride are increasingly seen in Massachusetts. Between September 2005 and November 2006, **5009 medicolegal investigations associated 107 deaths with licit or illicit fentanyl use, along with a co-detection of an opiate/opioid or cocaine/benzoyllecognine, or both.** Deaths associated

with illicit fentanyl use occur in younger people (39.4 vs. 61.5 years) with higher fentanyl (17.1 ng/mL vs. 4.4 ng/mL) and lower morphine (76.9 ng/mL vs. 284.2 ng/mL) postmortem blood concentrations, and more frequent cocaine co-intoxication (65% vs. 3%), than deaths associated with illicit fentanyl use. A wide range of postmortem blood concentrations of fentanyl was detected (trace-280 ng/mL), with a minimum concentration of 7 ng/mL of fentanyl strongly associated with illicit use of fentanyl in poly-drug cases. **The most commonly detected opiates/opioids in illicit fentanyl users were: morphine (29%), oxycodone (14.5%), and methadone (14.5%). Ethanol, cannabinoids, diazepam, citalopram, and diphenhydramine were each detected in greater than 10% of the licit fentanyl cases. Most fentanyl abusers died at their own home and their deaths were most often classified as accidental.** Mapping of primary residences of decedents revealed conspicuous clustering of the illicit fentanyl use cases, as opposed to the random pattern in licit use cases. Fentanyl misuse is a public health problem in Massachusetts.[38]

Tjaderborn et al., in 2007, report on a study of mortality from use of **Tramadol**. Tramadol is an extensively used centrally acting analgesic and is **considered a safe drug devoid of many serious adverse effects of traditional opioids. However, recently, toxicity and an abuse potential of tramadol have been reported.** This study examined fatal unintentional tramadol intoxications among Swedish forensic autopsy cases between 1995 and 2005. All fatal intoxications were selected, in which toxic concentrations of tramadol (>1 microg/g femoral blood) had been detected, and where the forensic pathologist considered the intoxication unintentional and the fatal outcome at least partly explained by tramadol. Toxicology analyses, police reports, autopsy protocols and medical records were scrutinized. **A total of 17 cases (eleven men and six women) of fatal unintentional tramadol intoxications were identified.** For these cases the median age was 44 years (range 18-78 years) and the median tramadol concentration was 2.0 microg/g (range 1.1-12.0 microg/g). Other pharmaceutical substances, illicit drugs or ethanol were detected in addition to tramadol in all of these cases. In fact, intoxication with multiple drugs was considered the cause of death in 10 (59%) cases. However, in seven cases tramadol was the only substance present in toxic concentrations. A history of substance abuse was identified in 14 (82%) subjects and a present tramadol abuse in 8

(47%). These results suggest that fatal intoxications with tramadol may occur unintentionally and that subjects with a history of substance abuse may be at certain risk. Precaution is therefore warranted when prescribing tramadol in such patients.[39]

In 2007, Wysowski **found opioids among prescription drugs associated with cause of death.** **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.[40]

In 2008, Chugh et al. report on the effect of **methadone and sudden death**. BACKGROUND: Published case reports have associated the therapeutic use of methadone with the occasional occurrence of sudden cardiac death. Because of the established utility of this drug and with the eventual goal of enhancing safety of use, we performed a community-based study to evaluate this association. METHODS: During a 4-year period, we prospectively evaluated all patients who consecutively had sudden cardiac death and underwent investigation by the medical examiner in the metropolitan area of Portland, Ore. Case subjects of interest were those with a therapeutic blood level of methadone (<1 mg/L), and case comparison subjects were those with no methadone identified. Patients with recreational drug use or any drug overdose were excluded from either group. Detailed autopsies were conducted, including the detection and quantification of all substances in the blood. RESULTS: **A total of 22 sudden cardiac death cases with therapeutic levels of methadone (mean 0.48+/-0.22 mg/L; range 0.1-0.9 mg/L) were identified (mean age 37.0+/-10 years, 68% were male) and compared with 106 consecutive sudden cardiac death cases without evidence of methadone (mean age 42+/-13 years, 69% were male). The most common indication for methadone use was pain control (n=12, 55%). Among cases receiving methadone therapy, sudden death-associated cardiac abnormalities were identified in only 23% (n=5), with no clear cause of sudden cardiac death in the remaining 77% (n=17).** Among cases with no methadone, sudden death-associated cardiac abnormalities were identified in 60% (n=64, P=.002). CONCLUSION: The significantly lower prevalence of

cardiac disease in the case group implicates methadone, even at therapeutic levels, as a likely cause of sudden death. These findings point toward an association between methadone and occurrence of sudden death in the community. Clinical safeguards and further prospective studies specifically designed to enhance safety of methadone use are warranted.[41]

Clause et al., in 2008, studied the effect of opioid maintenance treatment and mortality. **BACKGROUND: Opioid maintenance treatment (OMT)** is generally considered to reduce mortality in opiate dependents. However, the level of mortality reduction is still uncertain. This study investigates mortality reductions in an "intention-to-treat" perspective including all dropouts. The mortality reducing effects of OMT are examined both within treatment and post-treatment. The study separates overdose and total mortality reductions. **METHODS:** The study is a prospective cross-registry study with up to 7 years follow-up. All opiate dependents in Norway who applied for OMT (a total of 3789 subjects) were cross-linked with data from the death registry from Statistics Norway. Date and cause of death were crossed with dates for initiation and termination of OMT, and subjects' age and gender. A baseline was established from the waiting list mortality rate. Intention-to-treat was investigated by analysing mortality among the entire population that started OMT. **RESULTS: Mortality in treatment was reduced to RR 0.5 (relative risk) compared with pre-treatment.** In the "intention-to-treat" perspective, the mortality risk was reduced to RR 0.6 compared with pre-treatment. The patients who left the treatment programme showed a high-mortality rate, particularly males. **CONCLUSIONS:** OMT significantly reduces risk of mortality also when examined in an intention-to-treat perspective. Studies that evaluate effects of OMT only in patients retained in treatment tend to overestimate benefits. Levels of overdose mortality will influence the risk reduction. Cross-registry studies as the current one are an important supplement to other observational designs in this field.[42]

In 2008, Gibson et al. **found opioid maintenance therapy to reduce long term mortality.** **AIMS:** To (i) examine the predictors of mortality in a randomized study of methadone versus buprenorphine maintenance treatment; (ii) compare the survival experience of the randomized subject groups; and (iii) describe the causes of death.

DESIGN: Ten-year longitudinal follow-up of mortality among participants in a randomized trial of methadone versus buprenorphine maintenance treatment. SETTING: Recruitment through three clinics for a randomized trial of buprenorphine versus methadone maintenance. PARTICIPANTS: A total of 405 heroin-dependent (DSM-IV) participants aged 18 years and above who consented to participate in original study. MEASUREMENTS: Baseline data from original randomized study; dates and causes of death through data linkage with Births, Deaths and Marriages registries; and longitudinal treatment exposure via State health departments. Predictors of mortality examined through survival analysis. FINDINGS: **There was an overall mortality rate of 8.84 deaths per 1000 person-years of follow-up and causes of death were comparable with the literature. Increased exposure to episodes of opioid treatment longer than 7 days reduced the risk of mortality; there was no differential mortality among methadone versus buprenorphine participants. More dependent, heavier users of heroin at baseline had a lower risk of death, and also higher exposure to opioid treatment. Older participants randomized to buprenorphine treatment had significantly improved survival.** Aboriginal or Torres Strait Islander participants had a higher risk of death. CONCLUSIONS: Increased exposure to opioid maintenance treatment reduces the risk of death in opioid-dependent people. There was no differential reduction between buprenorphine and methadone. Previous studies suggesting differential effects may have been affected by biases in patient selection.[43]

Illicit Drug Deaths

Watterson et al. provide a description of demographics and causes of death for opioid addicts in 52 community treatment programs from 1970 to 1973.[44]

In 1976, Velvart et al. reported kidney failure (analgesic nephropathy) resulting from addiction and leading to death is most frequently encountered among the population of the cities, and the German Swiss Cantons, as well as among people of protestant faith.[45]

In 1978, Desmond et al. **dispute heroin overdose as a contributory factor to death. They found a low correlation among amount of heroin used and death over a five year period.**[46]

In 1981, Zimney and Luke reported on two hundred eighty-seven deaths directly related to narcotic abuse occurred in the District of Columbia between July 1971 and December 1979. **Factors contributing to death in some cases included lack of opiate tolerance as well as the conjoint abuse of ethanol. Free morphine was identified more often in the blood of victims dying rapidly than in the blood of those with longer post-injection survival.** A statistically significant correlation between the number of heroin-related fatalities and the purity of heroin available to the user was observed over the 8 1/2-year study period.[47]

Joe et al., in 1982, examined mortality rates daily opioid drug users for a four-year period following treatment in community-based agencies located across the United States. A total of 179 of these addicts died during this follow-up period, yielding a death rate of 15.2 per 1,000 person-years at risk. **When adjusted for age, addict death rates were found to be three to 14 times higher than those in the general US population.** Life table analysis was also used to examine these rates in relation to client demographic, background, and treatment variables obtained prospectively, both prior to and during treatment. Age, alcohol use, and criminal history were positively associated with higher death rates. With regard to causes of death, age proved to be the only significant predictor; older addicts (over 30) had the highest percentages of deaths due to "natural" causes, while over three-fourths of the deaths among younger addicts were drug related or involved violence. [48]

In 1984, Barr et al. reported on the **differences in death among alcoholics and drug addicts.** They found excess mortality occurred only among those misusing alcohol or drugs at 2 yr; nonmisusers had expected death rates. Disease and violent deaths were excessive among alcoholics, but only violent deaths exceeded expectancy among drug addicts. Of the 108 deaths, 66 were excess deaths, attributable to substance misuse and the associated way of life. However, among the 254 who were not misusing on follow-

up, 19 died rather than the 51 who would have died if their mortality had been that of the persistent misusers.[49]

Deaths among addicts in Denmark were reported in 1988 by Kringsholm. In the period 1968-1986 a total of 1618 fatalities among drug addicts were investigated at the three University Institutes of Forensic Medicine in Denmark. The annual number rose from 5 in 1968 to 163 in 1980, thereafter there has been a gradual fall to 121 in 1986. About 80% were males. The average age has risen from 22/23 years in the early 1970s to 31 years in 1986, and the percentage of addicts with a duration of abuse more than 10 years has increased gradually; both facts indicate a decrease in the recruitment among the quite young. In the whole period morphine was abused, supplemented by various medicines. Amphetamine was abused in the first years and again in 1986. The percentages of addicts with an abuse of alcohol and of addicts dying after a period of abstinence lasting more than 1 year, respectively, have increased. No essential changes were observed regarding distribution of residence or of the cause and manner of death. In the poisoning cases the predominant drug of poisoning was morphine/heroin, in all the years constituting approx. 30-50%. **The second most frequent drugs of poisoning in the first half of the period was barbiturate, in the last half dextropropoxyphene and methadone. Only very few cases dying of cocaine poisoning were present and deaths due to so-called designer drugs have not been observed.**[50] There is also a 1994 follow up by Kringsholm. [51]

A comparison of alcoholic death and drug addict deaths from the New Jersey Medical Examiner were reported by Haberman and Natarjan in 1986. **Cases were classified as alcoholics or narcotics abusers according to the following criteria: any case record report of drinking problems or narcotics abuse, alcoholism or narcotics abuse indicated in the manner or cause of death or autopsy findings of liver change or pancreatitis due to alcoholism, or toxicology findings of narcotics (unless medically prescribed).** The age-eligible cases decreased from 710 in year 1 to 691 in year 2 and 643 in year 3. Decedents classified as alcoholics rose from 18% in year 1 to 25% in years 2 and 3. The proportions classified as narcotic abusers and those with both conditions were relatively constant, averaging 7 and 5%, respectively, over the 3 years.

Substance abuse itself was the manner of death for alcoholics and most of those with both conditions; 38% of the narcotics abusers were homicide victims. There were no appreciable demographic changes among substance abusers during this period.[52]

Wessel reported on **circumstances at time of death for institutionalized addicts** in Germany. The basic client sample was composed of 743 drug addicts of the opiate type who had been admitted into the institute's drug-free outpatient program from 1969 to 1982. In this program, 91 clients died during the observation period. In order to be able to judge the various backgrounds adequately, a multiply subdivided classification system was developed for the death cases. Each case was recorded in three main categories: manner of death, cause of death, and phase of addiction. This was a more elaborate procedure than those commonly used since; in general, such death cases are only subdivided into a few groups that differ little from one another. **Two manners of death predominated in this sample: accidents caused by poison (62%) and suicide (25%). Within in the various causes of death, poison cases prevailed (80%) and opiate intoxication (single or combined) was predominant (60%).** Concerning the phase of addiction two phases were distinguished: the actual drug addiction phase (65%) and the intramural stay in prison or a hospital (25%). There were no significant sex-related differences. Various combinations regarding the mechanism of lethal opiate intoxication of drug addicts were scrutinized, concentrating on three approaches: the lack of opiate tolerance after periods of abstinence, the synergistic effect of simultaneously taking other CNS-depressant drugs, and differences in concentration in the heroin used.[53]

Neonatal deaths in Australasia and New Zealand were reported in 1987 by Elwood et al. A retrospective analysis has been made of the outcome of pregnancy in 174 women abusing narcotics, managed by a specialist team from a drug-dependency antenatal clinic. These women were cared for through 182 pregnancies of greater than 20 weeks' gestation, resulting in 183 live and 5 stillbirths. **The majority of patients were enrolled in a methadone programme and stabilized on the drug before the third trimester.** The group was characterized by a high prevalence of previous obstetric and medical problems. The most common antenatal complications were preterm labour (24%) and anaemia (12%). Preterm delivery and small-for-gestational-age each occurred in a

quarter of pregnancies. The mean birth-weight for the group was 2,746 g +/- 721 g; mean +/- S.D. Eight perinatal deaths occurred (5 stillbirths, 3 neonatal deaths), giving a perinatal mortality rate of 43/1,000.[54]

In 1989, Costa and Vari **propose Endocarditis (inflammation of the inner layer of the heart), a serious complication which is one of the more common causes of death among drug addicts. The Authors report on several aspects of this illness in addicts, describing the etiological profile and the clinical manifestations in particular, which show clear dissimilarities when compared with infectious endocarditis in patients who are not addicts.**[55]

Graw et al. studied deaths in addicts, with the **question of suicide or accident.** The investigation is based on the evaluation of 87 fatalities arising from drug addiction in autopsy material at the Institute for Forensic Medicine, Tubingen. When considered individually there were 76 cases of intoxication, 10 deaths due to external forces and one death due to natural internal causes as a result of drug abuse. The investigation was mainly concerned with the differentiation between suicide or accidental death in the intoxication group. **Amongst the total of 76 cases we found 12 to be indisputable or probable suicides and 44 to be indisputable or probable accidents. The remaining 20 could not be classified with sufficient certainty. With the exception of the existence of a farewell letter there were no single meaningful differentiation criteria.** There are indications which in themselves are not strong pointers but which, when considered together, allow a cautious interpretation. Finally the question is discussed as to how far the character changes typical in drug addiction can be explained by a latent suicidal tendency with quoad vitam fatalistic indifference.[56]

An extremely high death rate for addicts who did not accept rehabilitation was reported by Grondblah and Gunne. During its first 20 years of existence a national Swedish methadone maintenance program received 174 heroin addicts. Program policy, with a massive emphasis on vocational rehabilitation, and outcome data are described. In 75% of the cases the subjects abandoned their drug abuse behavior and took up work while 25% were expelled from the program due to violation of rules. The stability of the

program was established by 14 yearly check-ups of the percentage working and studying, which remained about 80%. The tendency towards maturing out of addiction was low in Swedish heroin addicts (6%) as evidenced by a special study including a 6-year follow-up of 34 subjects fulfilling admission criteria. Half of this group received methadone, while the other half were randomly assigned controls. The death rate among controls was at least 73 times the expected for the age group studied (20-24 years), while 81% of those receiving methadone became free of drug abuse and vocationally rehabilitated. The control group also showed a high rate of drug abuse-related morbidity. Among 34 female heroin addicted prostitutes 71% abandoned drugs and street prostitution and took up regular work.[57]

Kaa et al. report on deaths by poisoning among addicts in Denmark. A material of 194 deaths from poisoning among drug addicts investigated in the Medico-Legal Institutes in 1984 and 1985 is described as regards type of poisoning, sex, age, housing etc.. This investigation is part of a Nordic project concerned with deaths from poisoning among young adults in the age group 15-34 years in the Nordic countries with particular attention to deaths from poisoning among drug addicts. **Cases of heroin/morphine poisoning constitute half of the deaths while legal drugs such as dextropropoxyphene, methadone and ketobemidone were the causes of death in 30% of the cases.** In approximately 40% of the cases of poisoning, alcohol was involved (blood alcohol concentrations greater than 0.5%). Deaths from heroin occurred most commonly in Copenhagen while deaths due to dextropropoxyphene were relatively most common in the provinces. Less than half (42%) of the drug addicts examined lived in Copenhagen.[58] Kaa has a follow up in 1993.[59]

Stentoft et al reported on deaths in Nordic countries with a focus on addicts. Of 315 deceased, 194 were drug addicts according to a specific definition of this term. Women accounted for 28% of all the fatalities investigated in the study and 24% of those in addicts. More than 90% of the deaths were caused by drugs, with ethanol as a contributory factor in approximately 40% of cases. **Deaths caused by heroin/morphine predominated, causing 50% of the deaths among drug addicts, but legal drugs, such as dextropropoxyphene, methadone and ketobemidone were also frequent causes of**

death in this group. In half the cases the concentration of morphine in blood following injection of heroin/morphine was found to be equal to or less than 0.5 mumol/kg, and in only about one-tenth of cases was the blood concentration above 2.0 mumol/kg.[60] The same group also reported by country.[61]

Deaths of addicts in Methadone Treatment were described by Gronbladh et al. The mortality within a cohort of 115 street heroin addicts was studied for 5-8 years using the Kaplan-Meier survival estimate technique. This differed markedly from the relatively low mortality of 166 comparable heroin addicts given methadone maintenance treatment (MT). The street addicts' mortality rate was 63 times that expected, compared with official statistics for a group of this age and sex distribution. **When 53 patients in MT were involuntarily expelled from treatment, due to violation of program rules, they returned to the high mortality of street addicts (55 times that expected).** A group of 34 rehabilitated patients who left MT with medical consent retained the low mortality of MT patients (their mortality rate was 4 times that expected). Despite this great improvement in survival, even patients in MT showed a moderately elevated mortality (8 times that expected), mainly due to diseases acquired before entering the treatment program. It is concluded that MT exerts a major improvement in the survival of heroin addicts.[62]

Deaths among Swiss addicts are discussed by Jeanmonod and Fryc. Violent deaths are of considerable importance among young adults, since they account for half the deaths in this age group (average age 26.4 years). **Suicide and accidents (both categories including drug overdoses) are the most frequent categories of deaths from non-natural causes,** while in the USA deaths by homicide are also of considerable importance. Current repressive policies have not brought the problem of drug addiction under control. Each year deaths by overdose among drug abusers occur. Nevertheless, 40% of deaths among drug addicts are from other causes, principally accidents and suicides.[63]

In 1990, Kaa et al. reported (again) on addict deaths in Denmark. A total of 229 deaths among drug addicts (194 men and 35 women) examined of the Institute of

Forensic Medicine, University of Aarhus during the period 1981-1988 is described. In 178 deaths, the cause of death was poisoning with a drug or illegal narcotic. **Alcohol was involved in nearly half of these deaths and was, in addition, the cause of death in 4% of the cases. Heroin or morphine were the causes of death in one third of the cases while dextropropoxyphene, methadone and ketobemidone were responsible for approximately half of the deaths.** Until 1986, dextropropoxyphene was the dominating drug whereas the number of methadone deaths was considerably greater in the latter half of the period investigated than in the first half. Amphetamine alone was rarely the cause of death but the drug was seen in an increasing number of deaths in recent years. Thus, amphetamine was found in one third of the deaths in 1988.[64]

Ott et al. studied two effects (Danish and British) of **over-the-counter sales of opioids**. During the period 1978-1986, annual sales of paracetamol in Denmark increased from 1 million defined daily doses (DDD) (3 g) to 47 million DDD, while the number of admissions and deaths from overdose increased from 26 to 202 and from 1 to 3-4, respectively. The corresponding figures for salicylates are a decrease in sales from 113 to 94 million DDD, an increase in admissions from 282 to 595, and an increase in deaths from 5 to 22. From 1 January 1984 paracetamol became available on an over-the-counter basis. The figures for 1983 and 1984 were an increase in sales from 14 to 28 million DDD, an increase in admissions from 114 to 198, and an increase in deaths from 0 to 4. **The number of deaths from opioid overdose remained constant at a value of about fifty during this period, the mortality per dose being about 20-fold higher than for paracetamol and salicylates. Dextropropoxyphene-related deaths increased twofold to 121 in 1986, with unchanged sales figures.** A campaign launched by the National Board of Health resulted in a reduction in the number of deaths from dextropropoxyphene to 66 in 1987. The main effect of over-the-counter release of paracetamol was a dramatic increase in sales, without the epidemic of deaths observed a decade ago in the UK. It is suggested that the higher mortality of paracetamol poisonings in the UK compared to Denmark is related to the dextropropoxyphene content of the combination product, which is not available in Denmark. From an epidemiological toxicological viewpoint such combinations are not justified.[65]

Ruttenber et al. reported on the **effect of alcohol on heroin related deaths**. Toxicology analyses and other forensic science data were used to examine the mechanisms through which ethanol increased the risk for death caused by injected street preparations of heroin. The authors studied 505 victims of fatal heroin overdose and compared subjects who had concentrations of blood ethanol greater than 1000 mg/L (n = 306) with those who had concentrations less than, or equal to 1000 mg/L (n = 199). We found significant negative correlations between concentrations of ethanol and morphine (a heroin metabolite) in blood ($R^2 = 0.11$, $P = 0.0001$ for log₁₀-transformed variables) as well as between concentrations of blood ethanol and bile morphine ($R^2 = 0.16$, $P = 0.0001$ for log₁₀ bile morphine versus blood morphine). Toxicologic evidence of infrequent heroin use was more common in decedents with blood ethanol concentrations greater than 1000 mg/L than in those with lower concentrations. **Our data suggest that ethanol enhances the acute toxicity of heroin, and that ethanol use indirectly influences fatal overdose through its association with infrequent (nonaddictive) heroin use and thus with reduced tolerance to the acute toxic effects of heroin.**[66]

Staub et al. describe an **analytical method for the determination of morphine**, the active metabolite of heroin, in post-mortem blood by HPLC with electrochemical detection. An extraction technique allowing the determination of free and total morphine (free morphine + morphine glucuronide) was used. Blood morphine levels in postmortem cases are reported and the ratio of free to total morphine was measured in 52 cases obtained at autopsy.[67]

Veljkovic et al. **suggest that a better investigation of narcotic related deaths may lead to more of them being defined as suicide rather than overdose.**[68]

Delveccio and Brancatto discuss the **mortality of heroin addicts and HIV positive patients** in Italy. One hundred and eighty-seven heroin addicts resident in Valle Seriana Superiore were monitored from July 1985 to July 1989. This sample was representative of a total population of drug addicts estimated at some 350 subjects, 90 of whom (48.1%) were HIV-positive in Elisa assays and Western blot control tests. Six patients (3.2%) died; 3 of whom (3%) were HIV-positive and 3 (3.3%) were HIVab-

negative. **The most frequent cause of death (59%) was heroin overdose, which occurred in both HIV-positive and negative subjects, showing that the fear of contracting the disease or its possible evolution is not a deterrent in modifying risk behaviour.** During the four years of the study, 5 (5.5%) of the HIV-positive patients developed confirmed AIDS. Only one patient died from AIDS, thus confirming the current risk of death as being 1.1% in seropositive patients. An increase in mortality due to AIDS is expected in the future, in line with the current prevalent mortality rate due to heroin overdose.[69]

Walsh reports **opioids to be a relatively minor cause of deaths in New South Wales.** Opioid drug accidental deaths were reviewed in coronial post-mortem files of the Newcastle City Morgue, New South Wales, between 1970 and 1987. There were 23 accidental deaths directly caused by opioids, with 19 deaths (83%) involving the use of heroin/morphine. Deaths on weekends/public holidays were over-represented compared with weekdays. In 14 cases (61%), the police notes suggested that help-seeking had been inappropriately delayed by people in the presence of the subject. In almost half the cases where blood alcohol analyses were performed, the results were positive with a mean of 0.14 g alcohol per 100 ml. For a shorter time period 1985-1987, opioid-related suicides were also examined. Data on the five subjects involved in the suicides suggested they were a different target group for prevention. Opioids appear to be a very much smaller cause of death than alcohol and tobacco in the Newcastle Area.[70] Brettel and Dobbertin report on deaths of drug victims in Austria. The documents of 154 drug victims dissected in the Centre of Legal Medicine of the University of Frankfurt am Main in 1987 and 1988 were examined by computer. The average age i.e. was 26 years, the share of women 23 per cent. **In 47 per cent the main cause of death was an overdose of heroin and in 48 per cent heroin was the first drug that was taken.** 58 per cent of the drug victims came from totally intact families.[71]

Pre HIV drug related deaths in New Zealand are reported by Dukes et al. A mortality study of 997 patients registered for treatment at the Wellington Drug Clinic since 1971 was undertaken by examining the New Zealand death records. Sixty-seven known deaths were reported. The mortality rates were increased 11.5 times under the age

of 25 years, and 5.8 times for age 25-34 years, but not significantly thereafter. There were 7 deaths from trauma, 8 from suicide, and 28 accidental deaths. Myocarditis was the cause of death in four cases. In the 28 drug-related deaths the principle drugs incriminated were dextropropoxyphene, barbiturates, chloral hydrate, methadone and other opiates. Twenty-one deaths were due to unrelated diseases. It was considered important to document mortality in intravenous drug users in the 'pre-HIV' era. This study demonstrates quite low death rates from opioid drugs themselves.[72]

In 1993 Davoli et al. reported on the **occurrence of overdose as a cause of death in IV drug users**. Overdose mortality is the major adverse health effect of drug injection. The potential determinants of overdose death are poorly understood; the aim of this study was to investigate risk factors for overdose mortality among intravenous drug users (IVDU). A cohort of 4200 IVDU attending methadone treatment centres in Rome during the period 1980-1988, was enrolled. Data were collected from clinical records. Vital status and cause of death were ascertained as of 31 December 1988. A matched case-control analysis within the cohort was performed to identify risk factors of death from overdose. All overdose deaths were included as cases and four controls, matched on year of birth and sex, were selected for each case from among the cohort members still alive at the time of death of the corresponding case. **In all, 81 deaths from overdose were identified as cases and compared with 324 controls. A high risk of overdose death occurred among subjects who left treatment compared with those still in treatment (odds ratio [OR] = 3.55, 95% confidence interval [CI]: 1.82-6.90).** The OR was particularly elevated in the first 12 months after drop-out compared with those retained in treatment (OR = 7.98, 95% CI: 3.40-18.73).[73]

Haberman et al. report on **relationships among HIV and drug users**. Patterns of HIV infection and IV drug use in 697 Essex and Hudson Counties, New Jersey, 1986-1987 Medical Examiner (ME) cases, aged 15-59 years, were examined. All cases had toxicology tests for drugs and had been autopsied. Postmortem stored sera were blind-tested and confirmed for the presence of HIV-1-antibody by the New Jersey Department of Health. All cases and IV drug users were dichotomized according to the presence/absence of HIV-1-antibody and were then analyzed for differences in

demographic and postmortem characteristics. Subjects were predominantly Black men aged 30-44 years; the 119 HIV(+) cases were even more likely to be Black or Hispanic and in the 30-44 age group. **Evidence of IV drug use and HIV(+) status were very highly correlated;** 86 of 181 IV drug users were HIV(+). There was a low rate of suicide among HIV(+) cases and IV drug users. Only 3 of 63 suicide victims were HIV(+), and they were the only IV drug users whose manner of death was certified as suicide. Cases with toxicology findings of both heroin and cocaine were most likely to be HIV(+), followed in order by those with heroin or cocaine alone present. Cocaine alone was the illicit drug most often present in toxicology tests on all cases. Among IV drug users, heroin with cocaine was most often present.[74]

In 1993, Hser et al. reported on a 24 year follow up of addiction treatment. **OBJECTIVE:** This study examined **longitudinal patterns of narcotics use**, other substance use, criminal involvement, morbidity, and mortality among narcotics addicts. **DESIGN:** A 24-year follow-up study. Data were obtained from admission records and two face-to-face interviews conducted in 1974-1975 and 1985-1986. **PARTICIPANTS:** Five hundred eighty-one narcotics addicts admitted to the California Civil Addict Program during the years 1962 through 1964. **RESULTS:** Most of this sample initiated narcotics use before age 20 years and had a mean age at program admission of 25.4 years. In 1974-1975, **13.8% of the sample died and 28.6% tested negative for opiates.** Corresponding rates in 1985-1986 were 27.7% and 25.0%, respectively. Substance use and criminal involvement remained high among this sample into their late 40s. In any given year during the 10 years prior to the 1985-1986 interview, less than 10% of the sample participated in community-based treatment programs such as methadone maintenance. Disability, long periods of heavy alcohol use, heavy criminal involvement, and tobacco use were among the strongest correlates of mortality. **CONCLUSIONS:** The results suggest that the eventual cessation of narcotics use is a very slow process, unlikely to occur for some addicts, especially if they have not ceased use by their late 30s.[75]

Rodriguez et al. **question the validity of government records for identifying drugs as a cause of death.** **BACKGROUND:** Deaths by acute reaction from drugs consumption (RAD) particularly heroine or cocaine, collected in routine mortality

statistics, have not changed substantially during the last ten years, whereas an specific collection system (State Information System on Drug-Abuse SISD) presented a great increase. For this reason, we try to measure the validity of drug-related deaths certificate. METHODS: The cause of death, corresponding to the persons, from 15 to 39 years of age, decreased in 1988 and residing in the Municipality of Madrid, registered in the Civil Register Decease Book and in the death Statistics Bulletins (DSB) was compared with the cause present in the autopsy report. RESULTS: A detection rate of 2.45% for the CR and 3.27% for the DSB were obtained. With the consequent correction, the RAD for this age group would be the second cause of mortality in the Municipality of Madrid and deaths related to circulatory and respiratory system would decrease in a great measure. CONCLUSIONS: **It is necessary to improve substantially the collection of this cause of death in mortality statistics if we want a correct measurement of drug abuse lethal effects and the effectiveness of control programs on this health problem.**[76]

In 1994, Oppenheimer et al. report excessive death rates in a 22 year follow up of persons treated in London. Data are presented on the 43 people who died over a 22-year follow-up period of a cohort of 128 heroin addicts drawn in 1969 from the newly opened London clinics. **The main causes of death were drug-related, with 18 deaths specifically determined as due to overdose, of which the great majority was among people being prescribed opiates at the time.** The mortality rate was a mean of 1.84% annually, and the excess mortality ratio was 11.9. This excess was highest at the beginning and varied over the period of study, appearing higher at the opening of the clinics and again in the mid-1980s. No sex differences in mortality rates were demonstrated but the excess mortality was concentrated at younger ages. No prediction of the 85 survivors could be made on the basis of length of heroin use prior to study intake, nor on age at intake.[77]

Chatham et al studied **suicidality among methadone patients**. Previous work has shown that suicide is a significant cause of death among substance abusers, including methadone-maintained clients, and that the prediction of suicidal ideation and behavior is difficult. Preliminary review of data collected at admission on a population of 438 methadone-maintained clients found 55 expressing some level of suicidal behaviors

during the course of treatment. These clients were compared with a randomly selected comparison group of 55 nonsuicide clients matched for gender and race/ethnicity on measures of psychological dysfunction, drug use, family dysfunction, and help-seeking behaviors. Results showed that at time of admission suicidal clients reported: 1) more psychological dysfunction as evidenced by higher levels of depression, social dysfunction, hostility, risk-taking, and previous thoughts of suicide; 2) less family support at the present time and during childhood; and 3) more help-seeking behavior as evidenced by self-referral, number of previous treatment episodes, attendance at self-help meetings, and higher scores on motivational measures of desire for help. Differences in preadmission drug-using behaviors were not found between the two groups.[78]

In 1995, Kjelsberg et al. **question if deaths of young abusers are suicide or accidental.** Of 1969 earlier adolescent psychiatric inpatients, 1792 (91%) were traced after a mean follow-up period of 15 years. Thirty-nine patients, 2.3% of the men and 2.0% of the women had died from drug overdoses. An additional 16 drug- and alcohol-related deaths had occurred. The overdose death rate increased significantly during the observation period. At the time of death, 28 (72%) of the 39 overdose cases received a diagnosis of opioid dependence, the rest had polysubstance dependence. Death was most often caused by opioids. **Comparing the 39 overdose cases with 39 surviving controls and 35 suicides from the same patient population, we found that the suicide cases had more psychotic symptoms, suicidal ideation, learning difficulties and somatic disorders. The suicide cases received less follow-up treatment on discharge from hospital, did not enter specific drug treatment programs, and were the only ones to be discharged to the street.** We found no significant differences between the overdose cases and their surviving controls. Both groups showed poor impulse control and risk-taking behavior more often than the suicide group. The study lends support to the hypothesis that the majority of overdose deaths in young drug addicts are accidental poisonings and not misclassified suicides.[79]

Rosow and Kielland studied deaths of drug abusers in Denmark. **Current drug abusers in Norway seem to differ from those of 25-30 years ago in several respects, namely with regard to selection to drug abuse, living conditions, and the social**

responses to drug abuse. These factors may all be relevant for morbidity and mortality. Mortality and excess mortality under the age of 50 was assessed on the basis of data on 1,491 drug abusers admitted to the National Clinic for Drug Abusers (Statens klinikk for narkomane) during the years 1961-91. A significant excess mortality among the drug abusers was found for both genders, in all age groups and for all three decades. Males displayed a higher mortality than females, and the mortality among drug abusers increased with increasing age. Excess mortality was higher for women than for men and decreased with increasing age. **The most prevalent causes of death were overdoses, suicides and accidents. Mortality from overdoses and diseases was higher among persons admitted during the 1970s and 1980s compared with persons admitted during the 1960s.** The results are discussed in light of the qualitative differences between the former and present populations of drug abusers in Norway.[80]

In 1998, Ghodse et al. report a **reduction in deaths of drug addicts in England.** BACKGROUND: Mortality in specified clinical populations has often been regarded as a measure of treatment effectiveness. This study examined time trends in mortality of drug addicts in the UK notified to the Home Office over a 27-year period. METHODS: The study was a longitudinal analysis of routine mortality data of a population of newly notified addicts from 1967 to 1993. Altogether, 92 802 addicts were newly notified during the study period, and they accounted for 687 673 person-years of observation. The main outcome measures were age-specific all-causes mortality; drug-related mortality; and age- and sex-specific standardized mortality ratios (SMR) 1967-1993. RESULTS: There were significant differences in death rates between the periods 1967-1976 (19/1000 person-years) and 1984-1993 (10.5/1000 person-years). Excess deaths were significantly higher among the 1967-1976 cohorts than in the 1984-1993 cohorts (SMR ratio = 1.80, 95% CI: 1.64-1.97). **The majority of deaths were drug-related, with those aged <45 years more likely to die of a drug-related cause than those older (OR = 6.29, 95% CI: 4.97-7.96).** CONCLUSIONS: It appears that service provision has some impact on all-causes mortality among opiate addicts. As services improved, there was a corresponding decline in mortality rates during the study period. Further preventive measures, however, should be devised to reduce drug-related deaths.[81]

Also in 1998, Hall et al report an **increase in drug deaths in Australia**. AIMS: To determine if there had been an increase in the rate of opioid overdose deaths between 1979 and 1995, and to describe the characteristics of persons who died of an opioid overdose. METHOD: Opioid overdose deaths were defined according to ICD-9 as deaths due to drug dependence (codes 304.0 and 304.7) and accidental opiate poisoning (code E850.0). Data were obtained from a national register of deaths compiled by the Australian Bureau of Statistics on: age at death, sex and jurisdiction of all such deaths between 1979 and 1995 inclusive. Mortality rates were calculated for each sex for the 15-24, 25-34 and 35-44 age groups. RESULTS: **The number of opioid overdose deaths rose from 70 in 1979 to 550 in 1995. The rate (per million of the population aged 15-44) increased from 10.7 to 67.0.** The increase was more marked among males than females, increasing 6.8 times among males (from 15.3 in 1979 to 104.6 in 1995) and 4.7 times among females (from 5.9 in 1979 to 27.9 in 1995). New South Wales consistently accounted for around a half of all male overdose fatalities and its overdose mortality rate was almost twice that in Victoria, and three times that in the remaining states. The average age at death for males increased from 24.5 years in 1979 to 30.6 years in 1995. The increase in overdose mortality was greatest among men and women aged 35 to 44 years, and 25 and 34 years. An analysis by birth cohort showed that 46% of male overdose deaths and 50% of female overdose deaths in the period occurred among those born between 1960 and 1969. Deaths among persons born between 1950 and 1959 accounted for 38% of male and 33% of female deaths. CONCLUSIONS: There has been a statistically significant increase in opioid overdose mortality between 1979 and 1995, most of it occurring among persons who initiated heroin use in the late 1970s and early 1980s. Recent initiations of heroin use among those born between 1970 and 1979 have begun to be reflected in an increased rate of opioid overdose deaths. If their mortality experience replicates that of earlier birth cohorts then opioid overdose mortality will continue to increase.[82]

In 2005, Sorensen et al. report on mortality between addiction program success and those who continued drug use. OBJECTIVE: To **compare the 15-year mortality of people with a history of opioid dependence that had achieved stable abstinence**, with the mortality associated with continued drug use. Another objective was to study the

influence of hospitalization with comorbid psychosis on the 15-year mortality.

METHOD: In 1984, 188 persons (122 men and 66 women) with a history of intravenous narcotics addiction were interviewed about their drug-use pattern. A registry-based follow-up continued through 1999 and mortality was assessed. Three 1984-drug-use categories were formed. In category 1, cohort members had achieved stable abstinence from drug use by 1984. Using Cox multiple regression analysis, we (i) estimated reduced mortality of category 1 drug users, and (ii) studied the influence of hospitalization with comorbid psychosis on mortality. **RESULTS:** About 32% had died during the 15-year follow-up. **The 15-year mortality associated with stable abstinence was reduced by 56% when compared with the perceived worst drug-use pattern.** Hospitalization for comorbid psychosis was not independently associated with mortality in this sample. When drug-use categories were compared with mortality expectations for the general population, the standard mortality rates (SMRs) were clearly elevated. Even in the stably abstinent drug-use category (category 1), SMR was significantly elevated by at least seven-fold in both genders. **CONCLUSION:** People who had achieved stable abstinence from injecting narcotics use were at lower risk of premature death than people with continued drug use. A residual observed excess mortality in people who had apparently achieved stable abstinence from drug use is consistent with the view of drug addiction as a chronic disease.[83]

Bargagli et al., in 2006, focus on the effects of opioid use on overall public health . **OBJECTIVE:** To estimate the mortality rates from drug-related deaths and other causes among problem drug users and population attributable risk of death due to opiate use in eight study sites in Europe. **METHODS:** Opiate users were recruited from drug treatment centres during the period 1990-1998 and deaths followed up through national or local mortality registries. Gender-specific overall mortality rate, proportion of deaths by cause (drug-related, HIV, other), standardized mortality ratios (SMRs), and the attributable risk fraction (ARF) were estimated. **RESULTS:** **Crude mortality rates varied from 1 per 100 person-years in the Dublin and London cohorts to 3.8 per 100 person-years in Barcelona. The highest drug-related mortality rate was 10 per 1,000 person-years in Barcelona; the rates were approximately 7 per 1,000 person-years in Denmark, London, Rome, and Vienna, and <3.5 per 1,000 person-years for the others cohorts.**

The mortality rate for AIDS was <2 per 1,000 person-years in all the cohorts except Lisbon, Rome, and Barcelona, for which it was approximately 6 per 1,000 person-years. The highest SMR among males was 21.1 in Barcelona, and among females the highest SMRs were 53.7 and 37.7 in Barcelona and Rome, respectively. In Denmark the ARF was 5%, whereas it was >10% in all other study sites and 24% in Barcelona.

CONCLUSION: Cohort mortality studies, especially in combination with estimates of prevalence, provide useful insights into the impact of opiate use on mortality across European countries and emphasize how preventing overall and drug-related deaths among opiate users can significantly improve the health of the population.[84]

In 2005, Jauncey et al. discuss the problems of identifying opioid related deaths by ICD code. The reported number of deaths caused by opioid use depends on the definition of an opioid-related death. In this study, we used Australian Bureau of Statistics (ABS) mortality data to illustrate how choice of classification codes used to record cause of death can impact on the statistics reported for national surveillance of opioid deaths. Using International Classification of Diseases version 10 (ICD-10) codes from ABS mortality data 1997-2002, we examined all deaths where opioids were reported as a contributing or underlying cause. For the 6-year period there was a total of 5,839 deaths where opioids were reported. Three possible surveillance definitions of accidental opioid-related deaths were examined, and compared to the total number of deaths where opioids were reported for each year. Age restrictions, often placed on surveillance definitions, were also examined. As expected, the number of deaths was higher with the more inclusive definitions. **Trends in deaths were found to be similar regardless of the definition used; however, a comparison between Australian states revealed up to a twofold difference in the absolute numbers of accidental opioid-related deaths, depending on the definition.** Any interpretation of reported numbers of opioid deaths should specify any restrictions placed on the data, and describe the implications of definitions used.[85]

In 2006, Darke et al. describe comorbid conditions of persons who died of opioid toxicity. To **determine levels of systemic disease among cases of death due to opioid toxicity.** DESIGN: Analysis of coronial cases. SETTING: Sydney, Australia. CASES: A

total of 841 cases of death due to opioid toxicity (1 January 1998-31 December 2002). FINDINGS: Ventricular hypertrophy was present in 5.9% of cases and severe coronary artery atherosclerosis in 5.7%. Severe coronary pathology was more pronounced among older cases. Pre-existing bronchopneumonia was present in 13.2% of cases. Hepatic pathology was the most common type of pathology, and was far more marked among older cases. Cirrhosis was present in 25.3% of those aged > 44 years. Levels of renal pathology were comparatively low, but were related significantly to increasing age. Systemic disease in more than one organ system was present in 24.4% of cases, and was related to increasing age (44% of those aged > 44 years). The only pathology for which gender was an independent predictor among opioid cases was ventricular hypertrophy, more common in males. CONCLUSIONS: **Systemic disease, most prominently liver disease, is common among fatal opioid toxicity cases, and may be a factor in understanding the dynamics and age demographics of opioid-related death.**[86]

Eckberg et al. discuss the relationship between drug abuse in suicide in Denmark. This 5-year follow-up study includes all patients (n = 934; 50% females) treated for self-poisoning in Oslo during 1 year. Seventeen percent were considered suicide attempts upon admission, 25% among the nonabusers and 8% among the abusers. At follow-up, 122 patients were dead (61% males). **The mortality rate was highest among the abusers.** The mortality rate was similar (13%) among those who were considered to be suicidal on admittance and those who were not. The causes of death were suicide (28%), opiate abuse (16%), heart disease (14%), accidents or wounds (11%), alcoholism (9%) and others (22%). The standard mortality rate was highly increased in all groups (8 times on average), highest among the female opiate abusers, whose rate was 63 times higher than expected. The increased suicide rates (87 times for females, 27 times for males), however, may be a more relevant measure of mental morbidity than the standard mortality rate. Logistic regression analysis demonstrated that male sex, age above 50 years and the lowest social group were factors on admission associated with death in the follow-up period. Age above 50 years and suicidal attempt on admission were associated with subsequent suicide. The study strongly supports the idea of self-destructiveness and slow suicide in substance abuse.[111]

A reduction in opiate tolerance is suggested as influential in opiate-related deaths by Filseth et al. The study is based on autopsies of 86 drug addicts who died during the period 1986-88 after an opiate ingestion. The average postmortal concentration of morphine after ingestion of heroin was 0.88 $\mu\text{mol/l}$ blood, ranging from 0.0 to 3.1 $\mu\text{mol/l}$, which is substantially lower than values that have been reported from patients receiving morphine intravenously as an analgetic. **Postmortal blood concentrations of morphine were significantly lower among deceased with only fresh needle marks than among deceased with both old and fresh needle marks, suggesting that a pause in the drug abuse may have led to a decrease in opiate tolerance.** There was no relationship between the detected organ pathology finding of other ingested substances and the postmortal concentration of morphine. In 20% ($n = 17$) of the deceased the HIV-antibody test was positive and the average blood concentration of morphine was higher in this sub-population than in the rest of the cases.[112]

Neonatal Deaths

The earliest cited article (1975) reports a study of malformed fetuses related to opioid use in hamsters. [87]

Rajegowda et al. found a significant correlation among SID related deaths and narcotic addicted mothers. In regard to animal experiments, Lichtblau and Sparber found data to **question the validity of animal experiments which purport to be models for methadone maintenance programs but in which treatment is started immediately prior to or soon after conception.** They also suggest that withdrawal in utero may be responsible for many of the adverse effects of opiates on human and animal development.[88]

Fetal and neo-natal deaths related to opiate addict mothers were researched by Stauber et al. They found that **despite endocrine problems pregnancies do occur and are high risk pregnancies because of hepatitis, venereal disease, malnutrition,**

phlebitis, abscesses, premature deliveries, premature rupture of the membranes, mal-presentations, dysmaturity, pre-eclampsia, and numerous other social and psychological problems. Because of the varying content of heroin on the black market the fetus runs the risk of acute overdose or withdrawal. Withdrawal results in extremely marked fetal movements, with increased oxygen consumption and a danger of intra-uterine asphyxia sometimes resulting in intra-uterine fetal death. Most newborns develop a withdrawal syndrome with irritability, high pitched cries, shivering, tachycardia, perspirations, fever and generalized seizures.[89]

In 1985, Finnegan found neonatal results similar to Stauber above. **Infants born to opiate-dependent women frequently have low birth weights and low 1- and 5-min Apgar scores.** Significant postnatal problems, excluding neonatal withdrawal, can include jaundice, infection, aspiration pneumonia, transient tachypnea, and hyaline membrane disease. Neonatal abstinence may be severe and persist for as long as 3 months. Abstinence symptoms can include central nervous system hyperirritability, gastrointestinal dysfunction, respiratory distress, tremors, fever, high-pitched cry, increased muscle tone, uncoordinated sucking and swallowing reflexes, dehydration, and possible electrolyte imbalance. During the first week of life, increased respirations associated with hypocapnia and alkalosis may occur.[90]

The topic of SIDs and opioids was discussed in 1988 by Ramabadran and Bansinath. **Milk from breast or baby formula is the exclusive source of nutrition for newborn infants. Short chain opioid peptides such as beta-casomorphins have been isolated from breast milk as well as baby formula. These biologically active peptides are absorbed from the gastrointestinal tract. In infants predisposed to respiratory apnea because of abnormal autonomic nervous system development and respiratory control mechanisms, opioid peptides derived from milk might be one of the etiological factors for sudden infant death syndrome and near miss sudden infant death syndrome.**[91]

Lam et al. describe heroin addicted pregnancy complications in Hong Kong. A retrospective case controlled study was carried out on 51 Chinese gravidas who had

abused narcotics and who were delivered in a teaching hospital in Hong Kong. Heroin was the most commonly abused drug. The number of patients who changed from heroin to methadone was small. The major antenatal complications were late antenatal booking (average 28 weeks), prematurity (41%), small for gestational age baby (27.5%), antepartum haemorrhage (13.7%) and high prevalence of venereal disease (23.5%). **The babies born to drug addicted mothers were on average 629 g lighter at birth, 5 cm smaller in head circumference and 7 cm shorter in body length. Neonatal withdrawal symptoms occurred in 83% of all drug exposed neonates. The perinatal mortality rate was 19.6 per 1,000 total birth which was 2.5 times that of the control group.** There was one maternal death in our series. Drug addiction in pregnancy poses a major risk to both mother and child.[92]

In 1994, Hanssler and Roll reported found **withdrawal a major problem for infants of mothers using drugs and the possibility of Thrombocytoses involvement in SIDS.** In a retrospective study we analyzed clinical findings and hematological data of 16 neonates born from mothers using methadone and other drugs during pregnancy. Most infants presented with symptoms of drug withdrawal and needed medication. Hemoglobin concentration and leucocyte counts were within normal limits, whereas all infants showed thrombocytosis after the first week of life with thrombocyte counts (median) of 566,750 (week 2), 628,500 (week 3), 629,500 (week 4), 617,000 (week 5) and 639,150/mm³ (week 6). No thrombocytosis was found in 18 normal control infants which showed significantly lower platelet counts during the first days ($p < 0.05$) and by the second week of life ($p < 0.001$). The cause of this phenomenon is not known. Sudden infant death syndrome occurred in 1 infant. There are speculations that the high incidence of SIDS in this group of patients could be explained by thromboembolic complications in some of the cases.[93]

In 1997, Ostrea et al. report on mortality of exposed infants. **OBJECTIVE:** To determine the mortality rate, during the first 2 years of life, in infants who were exposed to cocaine, opiate, or cannabinoid during gestation. **METHODS:** For a period of 11 months, a large group of infants were enrolled and screened at birth for exposure to cocaine, opiate, or cannabinoid by meconium analysis. Death outcome, within the first 2

years after birth, was determined in this group of infants using the death registry of the Michigan Department of Public Health. **RESULTS: A total of 2964 infants was studied. At birth, 44% of the infants tested positive for drugs: 30.5% positive for cocaine, 20.2% for opiate, and 11.4% for cannabinoids. Compared to the drug negative group, a significantly higher percentage ($P < .05$) of the drug positive infants had lower weight and smaller head circumference and length at birth and a higher percent of their mothers were single, multigravid, multiparous, and had little to no prenatal care. Within the first 2 years of life, 44 infants died: 26 were drug negative (15.7 deaths per 1000 live births) and 18 were drug positive (13.7 deaths per 1000 live births). The mortality rate among cocaine, opiate, or cannabinoid positive infants was 17.7, 18.4, and 8.9 per 1000 live births, respectively.** Among infants with birth weight ≤ 2500 g, infants who were positive for both cocaine and morphine had a higher mortality rate (odds ratio = 5.9, confidence interval [CI] = 1.4 to 24) than drug negative infants. Eleven infants died from the sudden infant death syndrome (SIDS); 58% were positive for drugs, predominantly cocaine. The odds ratio for SIDS among drug positive infants was 1.5 (CI = 0.46 to 5.01) and 1.9 (CI = 0.58 to 6.2) among cocaine positive infants. **CONCLUSION:** We conclude that prenatal drug exposure in infants, although associated with a high perinatal morbidity, is not associated with an overall increase in their mortality rate or incidence of SIDS during the first 2 years of life. However, a significantly higher mortality rate was observed among low birth weight infants (≤ 2500 g) who were positive for both cocaine and opiate.[94]

Partridge and Wall studied the **use of opioids for infants withdrawn from life support**. **OBJECTIVE:** To determine the frequency of opiate analgesia administration to infants when life support is discontinued and to determine whether infant characteristics, such as birth weight and diagnosis, or the physician's reasons for discontinuing life support influence either the decision to provide opioid agents or the dosages administered. **METHODS:** We reviewed all 165 deaths in a 3-year period at a university-based level III intensive care nursery. Of the 121 deaths attributable to withdrawal or withholding of mechanical ventilation and/or extracorporeal membrane oxygenation, we ascertained whether opioid analgesics (morphine sulfate [MS] or fentanyl) were administered either concurrent with or after life-support withdrawal and at what doses.

We examined whether these end-of-life practices varied according to birth weight, diagnoses, and the reasons documented by the neonatologist for discontinuing life support. **RESULTS: Opioid analgesia was provided to 84% of infants as their life support was either withheld or withdrawn. Infants with necrotizing enterocolitis and major anomalies or chromosomal disorders were more likely to be given opiates than infants with other diagnoses.** Birth weight was not different for infants who received opiates compared with those who were not given opiates. Opioid analgesia was provided to all 18 infants for whom physicians documented the patients' suffering as a reason to discontinue life support. Sixty-four percent of infants who received opiates were given doses in the usual pharmacologic range of 0.1 to 0.2 mg/kg MS. Of the 36 infants given more than 0.2 mg/kg MS, all but 2 were receiving ongoing treatment with opioid agents. **CONCLUSIONS:** In most cases of withholding or withdrawal of life support in critically ill infants, neonatologists provided opioid analgesia to these infants at the end of life, despite the potential respiratory depression of opioid agents in infants whose respiratory support is discontinued.[95]

In 1998, Dasche et al. found that **addiction treatment for pregnant women may not harm the infant.** **OBJECTIVE:** Opioid withdrawal has been associated with poor fetal growth, preterm delivery, and fetal death. We sought to evaluate the safety of antepartum opioid detoxification in selected gravidas. **METHODS:** Between 1990 and 1996, women with singleton gestations who reported opioid use were offered inpatient detoxification. Predetoxification sonography was performed to confirm gestational age and to exclude fetuses with growth restriction and oligohydramnios. Women with mild withdrawal symptoms were given clonidine initially, and methadone was substituted if symptoms persisted. Objective signs of withdrawal were treated with methadone from the outset. Antenatal testing was performed once gestations reached 24 weeks. Newborns were observed for signs of neonatal abstinence syndrome and were treated as necessary. Obstetric and neonatal outcome data were collected. **RESULTS: Thirty-four gravidas elected to undergo opioid detoxification at a mean gestational age of 24 weeks. The median maximum dose of methadone was 20 mg per day (range 10-85 mg), and the median time to detoxification was 12 days (range 3-39 days). Overall, 20 women (59%) successfully underwent detoxification and did not relapse, ten (29%) resumed**

antenatal opioid use, and four (12%) did not complete detoxification and opted for methadone maintenance. There was no evidence of fetal distress during detoxification, no fetal death, and no delivery before 36 weeks. Fifteen percent of neonates were treated for narcotic withdrawal. CONCLUSION: In selected patients, opioid detoxification can be accomplished safely during pregnancy.[96]

Hall et al., in 2005 report on the effects of medication on neonate hypertension. OBJECTIVES: Hypotension occurs commonly among preterm neonates, but its cause and consequences remain unclear. Secondary data analyses from the NEOPAIN trial identified the clinical factors associated with hypotension and examined the contributions of morphine treatment or hypotension to severe intraventricular hemorrhage (IVH) (grades 3 and 4), any IVH (grades 1-4), or death. METHODS: In the NEOPAIN trial, 898 ventilated neonates between 23 and 32 weeks of gestation were enrolled, with equal numbers randomized to receive masked morphine or placebo infusions. Additional doses of open-label morphine were administered as necessary by medical staff members. IVH was diagnosed with centralized readings of early and late cranial ultrasonograms. Hypotension was assessed before study drug infusion, during the loading dose, and at 24 and 72 hours during study drug infusion. Logistic regression analyses with stepdown elimination identified the predictor factors associated with the hypotension, severe IVH, any IVH, or death outcomes at each time point. RESULTS: **Hypotension was associated with 23 to 26 weeks of gestation, morphine infusions, severity of illness, additional morphine doses, and prior hypotension.** Severe IVH was associated with shorter gestation, higher Clinical Risk Index for Babies scores, no prenatal steroids, pulmonary hemorrhage, hypotension before the loading dose, and morphine doses before intubation and at 25 to 72 hours. Neonatal deaths were associated with 23 to 26 weeks of gestation, higher Clinical Risk Index for Babies scores, pulmonary hemorrhage, patent ductus arteriosus, thrombocytopenia, and hypotension before the loading dose. Morphine infusions were not a significant factor in logistic models for severe IVH, any IVH, or death. CONCLUSIONS: Preemptive morphine infusions, additional morphine, and lower gestational age were associated with hypotension among preterm neonates. Severe IVH, any IVH, and death were associated with preexisting hypotension, but morphine therapy did not contribute to these outcomes. Morphine infusions, although they cause

hypotension, can be used safely for most preterm neonates but should be used cautiously for 23- to 26-week neonates and those with preexisting hypotension.[97]

In 2006, Fajemirokun-Odudey et al. report on effects of opiate use during pregnancy. **BACKGROUND: Opiate use in pregnancy is on the increase.** There are a number of complications associated with this problem but current data from UK centres are sparse. **DESIGN:** A retrospective study. **SETTING:** A North of England Hospital. **METHODS:** Maternal and neonatal case records were studied and a standard data set completed. **MAIN OUTCOME MEASURES:** Maternal and neonatal outcomes were classified by the woman's drug usage at the end of pregnancy. **RESULTS:** One hundred and ten babies born to 108 women were studied and 41% had evidence of previous exposure to the hepatitis C virus. Women who took heroin in later pregnancy were significantly more likely than women who were stabilised on methadone to have a baby who needed morphine (40% versus 19%), had higher mean maximum neonatal abstinence scores (NAS) (5.8 versus 4.7) and stayed in the neonatal unit significantly longer (mean 17.2 days versus 11.8 days). There were two neonatal deaths and the overall rate of prematurity was 29%. **CONCLUSIONS: The outcome for pregnancy in women who use opiates is complicated by high rates of prematurity and neonatal death. Women who used heroin in later pregnancy had babies who developed more severe NAS and needed a longer hospital stay than women who used only methadone.**[98]

In 2007, Kahlert et al. find strong association between use of opioids during pregnancy and SIDS. **OBJECTIVE:** This study was undertaken to determine the role of **opiate use during pregnancy as a predisposing factor for sudden infant death syndrome (SIDS) in infants born to HIV-infected mothers.** **METHODS:** In order to identify all infant deaths and their cause and association with maternal opiate use, the data of a nationwide prospective cohort study of HIV-infected mothers and their children were extracted and analysed for a 13-year period. **RESULTS:** 24 (5.1%) infant deaths were observed out of 466 infants followed up until death or at least 12 months of life. 3 (0.6%) of them were due to non-accidental trauma and were not associated with maternal opiate use. 7 (1.5%) died due to SIDS, which was confirmed by autopsy. All SIDS cases

occurred in infants born to mothers reporting use of opiates during pregnancy (n = 124). **The relative risk of SIDS compared to the general population was 18 (95% CI 9 to 38) for all infants of HIV-infected mothers, and 69 (95% CI 33 to 141) for those with intrauterine opiate exposure (p<0.001).** CONCLUSIONS: Compared to the Swiss general population, the risk for SIDS in this cohort of infants born to HIV-infected mothers was greatly increased, but only for mothers reporting opiate use during pregnancy. This effect appeared not to be mediated by prematurity, low birth weight, perinatal HIV infection or antiretroviral drug exposure.[99]

In 2008, Binder et al. reported on associations of **several replacement therapy drugs and pregnancy outcomes.** OBJECTIVE: The aim of the study was to evaluate the effect of substitution therapy in heroin addicted pregnant women on the course of pregnancy, perinatal outcomes and course of the neonatal abstinence syndrome. DESIGN OF THE STUDY: A five-year randomised prospective comparative study METHODS: The study was carried out in the period of 2002-2007. The group of patients included 147 i.v. heroin-addicted pregnant women. All of them were outpatients of our Perinatal Care Unit. Their daily dose of heroin was approximately 1g. Later, 30 women were disqualified from the study for breaking the randomised criteria engagement. The substitution therapy in women who agreed to undergo it, started during the I. trimester of pregnancy. Finally, 47 heroin, 32 methadone and 38 buprenorphine addicted women were enrolled in the study. Birthweight of newborns was compared with the national birthweight tables. Severity and duration of neonatal abstinence syndrome (NAS) were evaluated by Finnegan s score scale. RESULTS: None of the women delivered before the end of 34th gestational week. We did not encounter any perinatal death or developmental defect. The lowest birthweight, the highest number of newborns with IUGR and the most numerous placental changes were found in the group of heroin-addicted women. The differences compared to the two groups receiving substitution therapy were statistically significant (p < 0.05). The severity and course of NAS were the most severe (p < 0.001) in newborns of women from the methadone group. CONCLUSION: Comparison of the groups of outpatients is in many ways questionable because of the restricted possibility of the patients' control. The lifestyle of addicted women has the same impact as the drug use alone. This is probably the main reason for differences in some of the monitored

parameters between individual groups. Based on our results we can state that substitution therapy provides pregnant women with the possibility of social stabilization and adequate prenatal care. substitution therapy decreases the street heroin consumption. **Methadone notably protracts the newborn's abstinence syndrome. With regard to this fact, attention has been recently focused on substitution with buprenorphine that seems to be from this viewpoint a more considerate option.**[100]

Topic Two: Palliative Care and Pain Treatment

This second topic was found in 1975 in the Twycross article concerning the relief of terminal pain.[101]

In 1979, Olesen et al. reported medicinal pain treatment in cancer and terminal conditions: nearly everyone can be maintained pain free until a few days before death. [102]

In 1981, Noyes commented on the treatment of cancer pain. Under-treatment of cancer pain results not only from the limited expectations of patients but also from the inadequate knowledge of many physicians. **Successful management of this pain requires awareness of the importance of emotional factors and detailed knowledge of various treatment options.** When indicated, analgesic drugs should be administered according to a regular schedule and in sufficient dose to prevent the emergence of pain. Psychological techniques including supportive psychotherapy, relaxation training, hypnosis, and the hospice milieu may contribute to a comprehensive approach to pain. Likewise, psychotropic drugs including phenothiazines and tricyclic antidepressants may be useful adjuncts when administered along with appropriate analgesic medication. [103]

McGivney and Crooks commented that care of terminally ill patients with severe chronic pain should provide treatment that permits these patients to close their lives with dignity and purpose. Analgesics, both opioid and nonopioid, are available and when properly used can provide effective relief of pain for most terminally ill patients. **It is incumbent on the physician and on all others who care for the dying patient with**

severe chronic pain to understand clearly the dynamics of the pain experience, the clinical pharmacology of analgesics, and the needs of the patient, family, and friends.[104]

In 1986, Goldberg et al. suggest that little systematic research has been reported on analgesic use in terminal cancer patients. They used the National Hospice Study and found patients in hospital based hospice programs were more likely than other patients to have an analgesic prescription and to have consumed analgesics. **Patients in hospice settings were more likely to consume analgesia orally and less likely to have "prn" (as needed) analgesic prescriptions. The amount of analgesic consumption was inversely related to age.**[105]

Motsch et al. report on a different delivery system for terminal cancer patients. Pain control can be achieved in many patients with conventional methods and analgesics. However, significant numbers of patients remain in pain. For these patients, **continuous intrathecal narcotics delivered by an external portable pump via a subcutaneous port, offer substantially improved pain control with minimal risk of serious systemic complications.** Duration of treatment in our 40 cancer patients lasted up to 11 months. Continuous intrathecal morphine or fentanyl relieved pain till death due to cancer. Supraspinal side effects of opioids were only seen during the first week of intrathecal narcotic treatment. No serious complications like meningitis or other infections were observed. Postmortem examination also could not detect changes of the cord or signs of arachnoiditis due to intrathecal narcotics or the implanted catheter.[106]

In 1989, Creagan and Wilkenson describe levels of pain care. **A systematic approach to identifying the cause of pain and rational use of drug therapy are keys to providing pain relief to cancer patients.** Aspirin, acetaminophen and nonsteroidal anti-inflammatory drugs are effective for mild to moderate pain, and they enhance the effectiveness of weak oral narcotics, such as codeine. For severe pain, morphine is the drug of choice. A variety of adjuvant drugs can be used to enhance the effect of narcotics and to treat specific side effects of the disease or of therapy. **For the terminally ill patient, a peaceful death with dignity should always be possible.**[107]

Pain control in Japan was reported by Tsuneto and Kashiwagiin 1989. They found **pain control is one of the most significant ways to enable terminally ill cancer patients to live full lives up until the moment of death.** Analgesic drug therapy is the mainstay of cancer pain management. It is effective in more than 90% of patients if used correctly: the right drug in the right dose at the right intervals. A thorough history should first be obtained and the patient examined carefully. For mild to moderate pain, a nonopioid analgesic such as nonsteroidal anti-inflammatory drug or acetaminophen should be prescribed for the patient. If and when this treatment no longer relieves the pain, the patient should receive a strong opioid such as morphine or buprenorphine, together with a co-analgesic, if appropriate. The patient must receive careful and frequent supervision to ensure that the treatment continues to match the pain effectively and to take precautionary measures against side effects.[108]

In 1991, Bonifant and Clark-Reynolds discuss the use of a specific drug, morphine sulphate tablets in hospice practice for palliative care.[109]

The use of slow release morphine was compared between those with cancer and those with advanced HIV disease in two retrospective studies covering a total of 512 patients at home was presented by Dixon and Higginson in 1991. **Pain was found to be less severe in HIV/AIDS but still requiring opioid use in over a third of patients of which 14% needed subcutaneous diamorphine infusion when seriously ill at home.** Slow release morphine was used by 45% of those with cancer and 17% of those with HIV/AIDS. It was found to be a simple and convenient preparation for use at home with most patients never needing more than 30 mg twice daily. Half the cancer patients prescribed slow release morphine were able to take it until the day of death.[110]

In 1992, Brescia et al. discuss pain, opioids and cancer. PURPOSE: Pain is a common and feared symptom for patients with incurable cancer. Comprehensive assessment provides the foundation for effective pain management, and data that clarify the relationship between pain and other relevant factors also facilitate this process. The main objective of the study was to develop a clinical data base for advanced cancer patients and to survey data to determine (1) pain severity at admission, (2) opioid use at

admission, (3) change in opioid use during the hospital stay, and (4) survival in the hospital. PATIENTS AND METHODS: Information was collected prospectively on 1,103 patients admitted and on 1,017 patients who died within 6 months of the study's end. Demographic and clinical data were recorded 72 hours after admission and soon after death or discharge. RESULTS: **Seventy-three percent of patients had pain at admission. Cancer of the cervix was frequently (68%) associated with severe pain, as were prostate (52%) and rectal/sigmoid tumors (49%). Severe pain was more probable in those with bone metastasis, those admitted from home, and in those younger than 55 years of age. The majority (71.7%) of patients had a stable dosing pattern, and only 4.2% of the patients required dose increases of at least 10% per day.** CONCLUSION: This study demonstrated the wide variability in opioid doses required. No reliable predictor of opioid requirement was identified, and this lack of predictability of cancer pain severity underscores the need for ongoing assessment.[113]

In 1993, Mercadante reported on a **pain relief method for pancreatic cancer patients that reduces the amount of opioids consumed.** Twenty pancreatic cancer patients were studied to assess the effectiveness and duration of celiac plexus block compared to traditional treatment with analgesics by considering the previous and subsequent consumption of narcotics until their death. After 1 week of therapy with NSAID-narcotic sequence according to the WHO method, 10 patients were continued on this treatment, while the other 10 patients underwent celiac plexus block. Subsequently analgesics were administered as in the patients not treated by the block. A visual analogue score and opioid consumption were used to calculate the effective analgesic dose at weekly intervals until death. Celiac plexus block made pain control possible with a reduction in opioid consumption for a mean survival period of about 51 days. Administration of only analgesics resulted in an equal reduction in VAS pain score until death, but with more unpleasant side effects than when using celiac plexus block.[114]

Crane reported in 1994 on a study of **alternate delivery of opiates in a hospice.** Administration of oral opioids is not always possible for terminally-ill patients. Obstruction, emesis, or inability to swallow frequently force us to seek alternative routes of administration. When the rectal route is contraindicated, impractical, or otherwise

rejected by the patient or caregivers, we must resort to the parenteral route. The purpose of this study has been to validate the effectiveness, manageability, and side effects of bolus infusions of opioids utilizing an indwelling subcutaneous butterfly needle. The retrospective chart review included a convenience sample of 50 patients enrolled in our home-based hospice program who required subcutaneous infusion of opioids at some point during their enrollment. The total number of patients served during this time was 112. In the majority of cases (88 percent), the indication was inability to swallow or difficulty swallowing, which was related to impending death. Morphine sulfate was the opiate used in 955 of the cases reviewed. The mean four-hourly dose was 14.3 mg, with a range of 5 to 60 mg. Pain ratings were recorded using a 0-10 scale, both prior to initiation of and during the use of subcutaneous injections. Of the 42 percent of patients able to indicate a pain rating (0-10 scale) all rated their pain at 2 or below while using the subcutaneous route. No objective signs of pain were noted by caregivers or hospice nurses in the 58 percent of patients who were unable to rate their pain. The mean duration of time the needle remained in place was 4.62 days, with a range of 1-26 days.[115]

Mercadante followed lung cancer patients. Sixty consecutive lung cancer patients referred to a palliative care service were followed until death to obtain specific information about the prevalence, characteristics and localization of pain. To determine the course of treatment, an **Opioid Escalation Index and Effective Analgesic Score** were calculated. The prevalence of pain was almost 90%. Chest and lumbar pain were the most common sites with a clear correlation between site and metastases for the chest. Somatic incident pain did not achieve good pain relief while patients with neuropathic pain did not show any particular disadvantage compared to those exhibiting somatic or visceral pain. Mean Opioid Escalation Index and percentage of pain control observed in lung cancer patients were similar to those recorded in the general cancer population.[116]

Siever comments on ethical problems of exceeding recommended opioid dosages. Optimal pain control in the dying child often requires aggressive opioid therapy that exceeds recommended parameters and may hasten death caused by respiratory depression. **For pediatric nurses caring for the dying child, the administration of potentially life-shortening analgesia gives rise to a number of ethical issues.**

Pediatric nurses often express concern that aggressive pain control is a form of euthanasia or fear the child will develop a drug dependence. Lack of clarity about the ethical obligations and professional responsibilities of nurses who administer potentially life-shortening analgesia may also contribute to the dilemmas surrounding such situations. If left unresolved, these issues can interfere with the nurse's ability to implement an appropriate pain regimen. To provide adequate pain control, pediatric nurses who care for dying children must accomplish the following: critically examine ethical issues and underlying principles; understand the phenomena of addiction, tolerance, and physical dependence; and identify the boundaries of acceptable nursing practice when administering potentially life-shortening analgesia to terminally ill children.[117]

In 1995, Cherney et al summarize **methods of pain control in cancer patients.** BACKGROUND. This survey documents the strategies used by pain control physicians in the selection of opioid drugs and routes of administration in the management of inpatients referred to a cancer pain service. METHODS. The following approaches were prospectively evaluated during the treatment of 100 consecutive inpatients: 1) the influence of the evaluation of the goals of care on decision making, 2) selection of opioid drugs, 3) indications for changing opioid drugs and the frequency with which this strategy is used, and 4) selection of route of administration. RESULTS. Eighty of the 100 patients underwent a total of 182 changes in drug, route, or both drug and route before discharge or death. **The major reasons for change were to improve the convenience of treatment regimen in the setting of adequate pain relief (31.4%), diminish side effects in the setting of controlled pain (25.0%), reduce the invasiveness of therapy in the setting of controlled pain (19.3%), and simultaneously improve pain control and reduce opioid toxicity (17.7%).** When opioid toxicity was the reason for change, **physicians changed the opioid drug in 71% of cases and the route in 29%.** When convenience or invasiveness were targeted, the physicians changed the route in 61% of cases and the opioid in 39%. Forty-four patients required one or more change in the opioid, and 20 required 2 or more changes (range, 2-6 changes). At the time of discharge (n = 82), morphine was more commonly selected than hydromorphone or fentanyl (39% vs. 23% vs. 17%) and the routes of administration were oral (57%), transdermal (18%),

intravenous (18%), subcutaneous (5%), and intraspinal (4%). Therapeutic changes were associated with improvement in physician-recorded pain intensity and a lower prevalence of cognitive impairment, hallucinations, nausea and vomiting, and myoclonus among patients who were discharged from the hospital. **CONCLUSIONS.** These data illustrate the application of strategies for selections of opioid drugs and their route of administration that are recommended in current guidelines for the management of cancer pain.[118]

Gavrin and Chapman also summarize palliative treatment in 1995. Dying is universal, and death should be a peaceful time. Myriad comfort measures are available in the last weeks before life ends. Discussions about end-of-life issues often suffer from lack of informed opinion. **Palliative care experts have identified specific somatic and psychological sources of distress for dying patients and their loved ones. Pain, shortness of breath, nausea and vomiting, and fear of abandonment contribute substantially to both physical and psychological discomfort toward the end of life. Simple, effective methods exist for relieving those symptoms.** Knowledge about the natural events associated with dying and an informed approach to medical and psychological interventions contribute to systematic and successful comfort care. We describe the origin of physical and psychological distress at the end of life and provide strategies for alleviating many of the discomforts.[119]

Zech et al. report on the use of WHO guidelines in pain treatment. This paper reports on the experience gained using **World Health Organization Guidelines for cancer pain relief** over a 10-year period in an anaesthesiology-based pain service associated with a palliative care programme. The course of treatment of 2118 patients was assessed prospectively over a period of 140,478 treatment days. Non-opioid analgesics (WHO step I) were used on 11%, weak opioids (WHO step II) on 31% and strong opioids (WHO step III) on 49% of treatment days. Administration was via the enteral route on 82% and parenterally on 9% of treatment days. On the remaining days, either spinally applied opioids (2%) or other treatments (6%) were utilised. Fifty-six percent of the patients were treated with morphine. Morphine dose escalation was observed in about one-half of the patients being cared for until death, whereas the other

half had stable or decreasing doses over the course of treatment. Co-analgesics were administered on 37% of days, most often antidepressants (15%), anticonvulsants (13%) and corticosteroids (13%). Adjuvants to treat symptoms other than pain were prescribed on 79% of days, most commonly laxatives (42%), histamine-2-receptor antagonists (39%) and antiemetics (35%). In addition, palliative antineoplastic treatment was performed in 42%, nerve blocks in 8%, physiotherapy in 5%, psychotherapy in 3% and TENS in 3% of patients. A highly significant pain reduction was achieved within the 1st week of treatment ($P < 0.001$). Over the whole treatment period, good pain relief was reported in 76%, satisfactory efficacy in 12% and inadequate efficacy in 12% of patients. In the final days of life, 84% rated their pain as moderate or less, while 10% were unable to give a rating. Analgesics remained constantly effective in all 3 steps of the WHO ladder. Other clinical symptoms were likewise significantly reduced at 1 week after initial assessment, with the exception of neuropsychiatric symptoms. During the course of treatment, the latter were the major symptoms on 23% of days, followed by nausea (23%), constipation (23%) and anorexia (20%). Our results emphasise once again the marked efficacy and low rate of complications associated with oral and parenteral analgesic therapy as the mainstay of pain treatment in the palliative care of patients with advanced cancer. Wide dissemination of WHO guidelines among doctors and healthcare workers is thus necessary to effect a clear improvement in the treatment of the many patients suffering from cancer pain in the clinical and home setting.[120]

The topic of **euthanasia** appears in 1996. Butler et al. specifically address pain treatment. One of the most important components of a peaceful death is adequate control of pain and other distressing symptoms, such as dyspnea, agitation, and restlessness. **Pain is an important symptom in 75 to 80% of noncancer patients in the last year of life.** Opioid analgesics are often the mainstay of pain treatment for dying patients. A primary care physician also needs to know about anesthetic and neurosurgical approaches, the use of cognitive behavioral approaches, and the availability of specialized pain experts. A sizeable minority of physicians receive requests for an assisted death, which should be seen as a cry for help. The most useful function of advance directives is that they open an avenue for discussion between the doctor and the patient about a difficult subject.[121]

Also in 1996, Cavanaugh discusses the **ethics of life shortening drugs**. Double-effect reasoning is a nonconsequentialist analysis of a hard ethical case. In a hard ethical case, one can achieve some good end only if one also causes harm. Sometimes palliative analgesic administration to a terminally ill patient is a hard ethical case, for by it one relieves pain or distress while unavoidably hastening or causing the patient's death. **Is it ethically in the clear to administer an analgesic to relieve pain or distress knowing that one will hasten or cause the patient's death? Using double-effect reasoning, the author argues that death-hastening or death-causing palliative analgesic administration to a terminally ill patient is sometimes ethically in the clear and, at times, even obligatory.**[122] This topic is also addressed in 2000 by Hawlryluck and Harvey. The principle of double effect is widely used to permit the administration of narcotics and sedatives with the intent to palliate dying patients, even though the administration of these drugs may cause hastening of death. In recent medical literature, this principle's validity has been severely criticized, causing health care providers to fear providing good palliative care. **Most of the criticisms leveled at the principle of double effect arise from misconceptions about its purpose and origins.** This discussion will explore how virtue-based ethics can overcome the most important challenge to the principle of double effect's validity, that of its reliance on intention to determine whether the administration of analgesia is ethically acceptable.[123]

Folker et al. report on a survey of Danish physicians concerning **euthanasia**. In this survey we have investigated the experiences and attitudes of Danish physicians regarding end-of-life decisions. Most respondents have made decisions that involve hastening the death of a patient, and almost all find it acceptable to do so. Such decisions are made more often, and considered ethically more acceptable, with the informed consent of the patient than without. But both non-resuscitation decisions, and decisions to provide pain relief in doses that will shorten the patient's life, have been made and found acceptable by at least 50% of the respondents, even when there is no informed consent. Furthermore, 12% have doubled morphine dosages with fixed intervals, thus providing doses substantially higher than that necessary to control pain, without the informed consent of the patient. Two percent have helped in assisted suicide, and 5% have administered a lethal injection at the patient's request. Respectively 37% and 34% find

these last two practices ethically acceptable. Amongst those that do not find them acceptable, the most important reasons to be opposed are, the doctrine of double effect, the doctrine of doing and allowing, and the view that human life is sacred. Amongst supporters, the most important reasons mentioned are, that the patient's right to self-determination should be respected, the view that a patient should not be forced to suffer, and the view that the patient has a right to be helped to a dignified death.[124]

Meuret and Jocham discuss **Patient Controlled Analgesia (PCA)**. Patient-controlled analgesia (PCA) was administered in the domiciliary environment in 143 pre-terminally and terminally ill tumour patients suffering either from excruciating chronic pain or severe chronic/acute complex pain that could not be relieved adequately by oral analgesia. Morphine solutions were infused subcutaneously in concentrations between 1% and 3%. The intravenous route was preferred in patients with indwelling catheters or those susceptible to inflammatory skin reactions at the infusion site. After initial dose adjustment, lasting 2-3 days, the morphine amounts infused by PCA reached a median of 93 mg day⁻¹ (range 12-464 mg day⁻¹). The median was 28% lower than the median dose administered orally. A total of 84% of patients utilized the option of bolus self-administration. The median percentage administered via the bolus mode amounted to 5.3% of the total requirements. **During the course of treatment, morphine requirements increased by a median of 2.3 mg day⁻¹ (range -29 +52 mg day⁻¹).** **Most patients were treated continuously in the home care setting until death, the median duration being 27 days (range 1-437 days). The terminal morphine demands reached a median of 188 mg day⁻¹ (range 15-1008 mg day⁻¹).** **PCA turned out to be safe and effective, attaining excellent results in 95 (66%) patients and satisfactory pain relief in 43 (30%).** PCA proved to be insufficient in five (4%) cases. Side-effects were mild: constipation, fatigue, nausea and local inflammatory skin reactions occurred in 9%. Thus, with support from an experienced mobile nursing team, PCA can be safely administered in the terminal domiciliary care of tumour patients. PCA is superior to oral analgesia, especially in the treatment of severe oscillating pain. PCA provides adequate pain control in about 96% of patients who are poorly responsive to oral opioids.[125]

During 1997, Mercante et al. reported methods of monitoring cancer patients on pain therapy. Until now, there have not been any **parameters to monitor opioid therapy in cancer patients with pain**. In this study, 325 consecutive advanced cancer patients were scheduled for a prospective longitudinal survey. After exclusions, 67 patients were surveyed. All included patients were advanced cancer patients with pain that required opioid therapy for more than 6 weeks before death. Opioid escalation, symptoms associated with opioid therapy, pain mechanism, and pain intensity were recorded. Indices were calculated to categorize the response to opioids. The opioid escalation index (OEI) was used to index the mean increase of the starting opioid dosage, expressed as a percentage or in mg. The length of the period of stable dose (MLD) and the effective analgesic score (EAS), that is, the analgesic consumption/pain relief ratio calculated at fixed intervals, were also used. Patients with a mean visual analogue scale score (VAS) of less than 4 and regular OEI and EAS were considered responsive; patients with a mean VAS less than 4 but with an OEI more than 5 or increases of more than 100% of EAS when compared to that calculated the week before were considered mildly responsive; and patients with a mean VAS more than 4 were considered unresponsive. Advanced age, female gender, and previous chemotherapy were all factors reducing OEI. Head and neck cancer was associated with a higher OEI. Regarding the influence of the opioid-related symptoms, an increased OEI was associated with the presence of confusion. Moreover the presence of confusion was associated with neuropathic pain. Neuropathic pain taken alone, however, did not influence this score. Gender-specific cancer, such as breast cancer, influenced the gender differences reported for MLD (significantly longer than that reported for males and other primary tumor). Good responsiveness was observed in 28 patients, partial responsiveness in 33 patients, unresponsiveness in six patients. **Psychological factors were associated with poor pain relief, probably reducing the patient's compliance.** The tools used in this study may be useful in monitoring the effects of opioid therapy in cancer pain patients. Simple numbers are easy to compare and make it possible to profile opioid responsiveness and differences among patients.[126]

In 1998, Cooke et al. reported on **hastening death among HIV patients**.
OBJECTIVES: To determine the extent to which homosexual men dying of the acquired immunodeficiency syndrome (AIDS) receive medication intended to hasten death. To

assess the impact on caregivers of administering medications intended to hasten death. **METHODS:** In a prospective study of caregiving partners of men with AIDS (n = 140), characteristics of the ill partner, the caregiver, and the relationship were assessed at baseline and 1 month before the ill partner's death. Three months after the death, caregivers were asked if they had increased their partner's narcotic and/or sedative-hypnotic medication dose and if so, what had been the objective of the increase, and their comfort with their medication decisions. **RESULTS: Of 140 ill partners who died of AIDS, 17 (12.1%) received an increase in the use of medications immediately before death intended to hasten death.** Diagnoses and care needs of ill partners who received increases in the use of medications to hasten death did not differ from those of ill partners receiving medication for symptoms. Fourteen increases (10%) in use of medications were administered by caregivers. These caregivers did not differ from those administering medication for symptom control in level of distress, caregiving burden, relationship characteristics, or comfort with the medication decision, but they reported more social support and positive meaning in caregiving. **CONCLUSION: The decision to hasten death is not a rare event in this group of men. There is no evidence that it is the result of caregiver distress, poor relationship quality, or intolerable caregiving burden; and it does not cause excessive discomfort in the surviving partner.** This study, although small, has implications for the policy debate on assisted suicide.[127]

Guest et al. found that a **switch from weak to strong opioids did not have a major effect on cost of care.** **OBJECTIVE:** We constructed a UK-based decision model of palliative care for terminally ill cancer patients who were switched from a weak to a strong opioid so that the expected direct healthcare costs in the UK could be estimated from the time a patient commenced a strong opioid until death. **DESIGN:** Decision analysis techniques were used to estimate the expected total direct healthcare cost per patient, stratified according to the first choice of strong opioid. The model was based on prescription data on 1975 terminally ill cancer patients who were on the Intercontinental Medical Statistics database, Mediplus (IMS Ltd, Middlesex, England). Resource-use data were obtained from published literature, a Delphi Panel and an advisory panel with expertise in palliative care. **MAIN OUTCOME MEASURES AND RESULTS:** The expected cost of managing terminally ill cancer patients after they switched from a weak

to a strong opioid ranged from 2391 pounds sterling (Pounds) to 3701 Pounds at 1995/1996 prices, depending primarily on the patient's duration of survival. Sensitivity analyses showed that the cost could be as low as 1500 Pounds or as high as 6000 Pounds, depending on resource use (at 1995/1996 prices). The key cost drivers were: hospice care, hospitalization, general practitioner (GP) consultations and specialist nurse visits. In contrast, neither the choice of opioid nor managing constipation impacted substantially on the expected cost. Approximately two-thirds of the expected total cost was incurred by the UK National Health Service (NHS), with the remainder incurred by voluntary and charitable sectors. Hospice care and hospitalization collectively accounted for between 50 and 80% of the expected costs. Management of patients in the community by the primary healthcare team accounted for between 10 and 40% of the costs. The acquisition cost of opioids accounted for between 2 and 8% of the expected cost and discounting the cost of these drugs sold to hospitals did not impact substantially on the total expected costs. The use of other resources such as antiemetics, NSAIDS, antidepressants and gastrointestinal drugs accounted for up to 3% of the expected cost. CONCLUSION: The expected cost of palliative care in the UK healthcare setting ranged from approximately 2500 Pounds to 4000 Pounds (1500 Pounds to 6000 Pounds in the sensitivity analysis) depending on the length of survival after patients switch from weak to strong opioids. Since opioids account for only 2 to 8% of expected costs, factors other than economic issues, such as tolerability profile, patient preference and convenience of use, should form the basis of clinical decision-making between opioids with similar analgesic efficacy.[128]

During 1998, Mercadante et al **recommend Methodone over Morphine for terminal cancer patients**. PURPOSE: The aim of this study was to evaluate the analgesic and adverse effects and the doses of methadone in comparison to morphine. PATIENTS AND METHODS: A prospective randomized study was performed in a sample of 40 patients with advanced cancer who required strong opioids for their pain management. Patients were treated with sustained-release morphine or methadone in doses titrated against the effect administered two or three times daily according to clinical need. Opioid doses, adjuvant medications, symptoms associated with opioid therapy, pain intensity, and pain mechanisms were recorded. The opioid escalation indices in percentage (OEI%) and milligrams (OEImg) were calculated. The effective analgesic

score (EAS) that monitors the analgesic consumption-pain ratio was also calculated at fixed weekly intervals. **RESULTS: differences in pain intensity were found. Patients treated with methadone reported values of OEI significantly less than those observed in patients treated with morphine.** Seven patients in the methadone group maintained the same initial dosage until death, whereas only one patient in the morphine group did not require opioid dose escalation. A more stable analgesia in time in patients treated with methadone was shown by the low number of gaps in EASs reported. Symptom frequencies and intensities were similar in the two groups. **CONCLUSION:** Methadone is a drug of indisputable value in the treatment of cancer pain, and an unbalanced focus on the risks of inappropriate use rather than the benefits should not compromise the use of a relevant alternative to morphine in the management of cancer pain.[129] In a separate publication they also recommended dextropropoxyphene [DARvocet] over morphine. The role of opioids for moderate pain (so-called "weak" opioids) in the second step of the World Health Organization's analgesic ladder has been investigated in a prospective randomized study. Sixteen patients were administered dextropropoxyphene (DPP) in a dosage ranging from 120 mg to 240 mg daily (group 1), and 16 patients were administered the lowest doses (20 mg daily) of commercially available controlled-release morphine (group 2). Equianalgesic doses of oral morphine, pain relief, and symptoms during the first 10 days of therapy and during the last 4 weeks before death were assessed. Three of 16 patients maintained DPP until death, whereas three patients in group 2 were switched to DPP due to the occurrence of intolerable side effects. Intensity and frequency of nausea and vomiting, drowsiness, and dry mouth were higher in group 2 than in group 1 during the initial treatment. These results stress the role of "weak" opioids during the induction of opioid therapy in opioid-naive cancer patients.[130]

Morita et al. describe the death process and use of pain relief medications in 1998. To determine the physical and medical change in the dying process, a prospective study was performed on 100 terminally ill cancer patients. The mean (median) time from the onset of death rattle, respiration with mandibular movement (RMM), cyanosis on extremities, and pulselessness on the radial artery to death was 57 (23) hours, 7.6 (2.5) hours, 5.1 (1.0) hours, and 2.6 (1.0) hours respectively. Death rattle preceded the other

three conditions in 74 percent of the subjects, while RMM preceded cyanosis and pulselessness in 63 percent. The ratio of awake-drowsy-comatose patients was 56-44-0 percent one week before death, 26-62-12 percent in the last 24 hours, and 8-42-50 percent in the final six hours. **The number of opioid users and average dose increased significantly as death approached, from 42 percent and 49 mg/day (parental morphine equivalent) four weeks before death to 87 percent and 139 mg/day in the final 48 hours. The frequency of extra dosage also increased significantly, from 32 percent (opioid) and 40 percent (non-opioid) one week before death to 68 percent and 66 percent in the last 48 hours, respectively.** The change of physical signs and medical intervention when death is impending has a common pathway in spite of large individual variations; thus, understanding this nature can help clinicians to offer better palliative care to terminal cancer patients.[131]

In 1999, Daeninck and Bruera introduce neurotoxicity as a problem with opioid use for pain treatment. The majority of cancer patients develop pain before death. This pain has been shown to be underdiagnosed and undertreated. Opioid use has increased in the past 20 years in both developing and developed countries. **The changing pattern in opioid use has resulted in the emergence of neurotoxicity as a major side effect of the treatment of cancer pain.** The syndrome of opioid-induced neurotoxicity (OIN) encompasses delirium, hallucinosis, myoclonus/seizures and hyperalgesia. Increased vigilance can lead to the timely diagnosis of OIN, and strategies for its treatment can be implemented with encouraging results. Identification and modification of risk factors for the development of OIN can help in its prevention and improve the quality of life in advanced cancer patients.[132]

Rocker et al., in 2003, studied perceived comfort at end of life. **PURPOSE:** Most deaths in intensive care units (ICUs) follow a withdrawal of life support (LS). Evaluation of this process including the related perspectives of grieving family members is integral to improvement of palliation in the ICU. **METHODS:** A prospective, multicentre, cohort study in six Canadian university-affiliated ICUs included 206 ICU patients (length of stay \geq 48 hr) who received mechanical ventilation (MV) before LS withdrawal. We recorded modes, sequence and time course of LS withdrawal and drug usage (4 hr before;

4-8 hr and 8-12 hr before death). We asked a specified family member to assess patient comfort and key aspects of end-of life care. RESULTS: MV was withdrawn from 155/206 (75.2%) patients; 97/155 (62.6%) died after extubation and 58/155 (37.4%) died with an airway in place. **The most frequently used drugs and the cumulative doses [median (range)] in the four hours before death were: morphine 119/206, 24 mg, (2-450 mg); midazolam 45/206, 24 mg, (2-380 mg); and lorazepam 35/206, 4 mg, (1-80 mg). These doses did not differ among the three time periods before death. Of 196 responses from family members most indicated that patients were perceived to be either totally (73, 37.2%), very (48, 24.5%), or mostly comfortable (58, 29.6%).** Times to death, morphine use and family members' perceptions of comfort were similar for each type of change to MV. CONCLUSIONS: Most patients were perceived by family members to die in comfort during a withdrawal of LS. Perceptions of patient comfort and drug use in the hours before death were not associated with the mode or sequence of withdrawal of LS, or the time to death.[133]

Topic Three: Pharmacology, Psychology, Origins of Abuse

Chau and Harris reported in 1980 on the different effects of the d- and l-isomers of codeine.[134]

Also in 1980, Pasternak et al reported that Naloxazone treatment blocks the analgesic effects of morphine for at least 24 hours but does not prevent death from high doses of morphine.[135]

Coleman proposes a theory of understanding heroin abuse. This theory is based on the premise that death, separation, and loss are significant etiological factors in heroin-addict families. The death and death-related variables are integral parts of a homeostatic pattern that keeps the drug-abusing member helpless and dependent on staying at home with the family. Within the complex set of feedback mechanisms involved in the drug-taking process lies an overall sense of family hopelessness and lack of purpose or meaning in life which accompanies the repetitive drug-sustaining cycle of family interactions. [136]

Causes of addiction were reported by Rounsaville et al. who defined three groups : (a) an initial childhood trauma group; (b) an early delinquency group; and (c) an initial drug use group.[137]

In 1984, Pare et al. reported a study with the objective to correlate blood morphine concentrations to regional brain concentrations and indirectly to opiate receptor density. Brain sections obtained postmortem from 21 suspected heroin-associated fatalities were analyzed for morphine by gas chromatography with FID. In all of the cases where death was attributed to narcotic overdose the concentration of morphine was found to exceed the minimum fatal concentration, 0.2 microgram/g of tissue, in one or more of the brain sections, whereas the blood concentration exceeded 0.2 microgram/g in only five cases. The correlation between the concentrations in the thalamus and blood were very good, suggesting that the thalamus could be used to estimate blood morphine concentration by the forensic toxicologist.[138]

Rajs, Hors and Omstad conducted a forensic comparison of lung tissues from narcotic users and a control of persons not known to use narcotics. The addict group also exhibited myocardial alterations in 28 of 30 cases. Typical findings were myofibrillar degeneration and fatty infiltration. In 15 of 30 addicts morphological and toxicological examination did not yield a definitive cause of death. However, the present demonstration of cardiopulmonary pathology suggests that narcotic addicts may be prone to acute circulatory and/or respiratory derangement even if no overdose of drugs is taken.[139]

A significant finding of drug-drug interaction was reported by Poling et al. in 1985. Morphine and Tripeleminamine (anit-itch, antihistamine) were compared in mice. Neither drug alone produced death at any dose. Supra-additive effects were observed when the drugs were combined.[140]

In a British study of addicts, Edwards and Goldie reported a ten-year follow-up study of 74 opiate (most heroin) addicts referred to the Drug Dependence Clinic in Southampton showed that overall, little use was made of the treatment facilities available. Half of the patients on whom we were able to obtain follow-up data appeared to be no longer abusing drugs. An appreciable number of subjects had committed offences prior to

abusing drugs and a large proportion offended during the follow-up period, adding support to the view that most addicts are not driven to crime because they are unable to obtain the help they need. The death rate of 15% is that expected in a long-term follow-up study. The results suggest that the natural history of many heroin addicts is uninfluenced by therapeutic intervention.[141]

Hall et al. report drug-drug interactions on the effect of dezocine, an agonist-antagonist opioid analgesic, on enflurane MAC (EMAC) was measured in dogs. It is concluded that dezocine produces a dose-dependent reduction in EMAC limited by cardiovascular toxicity. This toxicity appears to be related to direct myocardial depression by high doses of dezocine in the presence of enflurane.[142]

Buchanan and Brown discuss designer drugs. 'Designer drugs' are substances intended for recreational use which are derivatives of approved drugs so as to circumvent existing legal restrictions. The term as popularised by the lay press lacks precision. Contrary to the popular belief that 'designer drugs' are original creations, the majority of these agents are 'borrowed' from legitimate pharmaceutical research. They merely represent the most recent developments in the evolution of mind-altering chemicals.[143]

In 1990, Jacobson et al. studied the effects of anaesthetics on eventual addiction. OBJECTIVE--To test the hypothesis that opiate addiction in adults might stem partly from an imprinting process during birth when certain drugs are given to the mother. DESIGN--Retrospective study by logistic regression of opiate addicts with siblings as controls. SETTING--Stockholm, Sweden. SUBJECTS--200 Opiate addicts born in Stockholm during 1945-66, comprising 41 identified during interviews of probands for an earlier study; 75 patients whose death from opiate addiction had been confirmed during 1978-88; and 84 accepted for the methadone programme. 262 Siblings (controls) born in Stockholm during the same period, 24 of whom were excluded for drug addiction or being brought up outside the family. Birth records were unavailable for eight, leaving 230 siblings and 139 corresponding probands. MAIN OUTCOME MEASURES--Administration of opiates, barbiturates, and nitrous oxide (for greater than 1 h) to mothers of all subjects during labour within 10 hours before birth as a risk factor for adult opiate

addiction. RESULTS--In subjects who had subsequently become addicts a significant proportion of mothers had received opiates or barbiturates, or both, compared with unmatched siblings (25% v 16%, $\chi^2 = 5.83$, $df = 1$, $p = 0.02$), and these mothers had received nitrous oxide for longer and more often. After controlling for hospital of birth, order of birth, duration of labour, presentation other than vertex, surgical intervention, asphyxia, meconium stained amniotic fluid, and birth weight the relative risk for offspring subsequently becoming an adult opiate addict increased with the number of administrations of any of the three drugs. When the addicts were matched with their own siblings the estimated relative risk was 4.7 (95% confidence interval 1.8 to 12.4, p for trend = 0.002) for three administrations compared with when no drug was given. CONCLUSIONS--The results are compatible with the imprinting hypothesis. Therefore, for obstetric pain relief methods are preferable that do not permit substantial passage of drugs through the placenta.[144]

In 1991, Hauser and Stiene-Martin report on the effects of opiates on glial development. Glial cells are non-neuronal cells that provide support and nutrition, maintain homeostasis, form myelin, and participate in signal transmission in the nervous system. The results suggest that the ability of opioids to modify glial growth is highly selective and varies depending on astrocyte type, as well as temporal and regional factors. Spatial and temporal differences in the response of developing glia to opioids may determine critical periods of CNS vulnerability to opioids in the maturing brain.[145]

Maneckjee and Minna found that methadone significantly inhibited the *in vitro* and *in vivo* growth of human lung cancer cells. The *in vitro* growth inhibition (occurring at 1-100 nM methadone) was associated with changes in cell morphology and viability detectable within 1 hr and was irreversible after a 24-hr exposure to the drug. These effects of methadone could be reversed in the first 6 hr by naltrexone, actinomycin D, and cycloheximide, suggesting involvement of opioid-like receptors and the requirement for *de novo* mRNA and protein synthesis. We conclude that the lung cancer growth inhibitory effects of methadone are significant, occur at low concentrations, and are

mediated by a nonconventional type of opioid binding site distinct from methadone receptors found in the brain.[146]

In 1993, Herd et al. describe a relationship between addiction and craving. Molecular changes in the neostriatum of human subjects who died with a history of cocaine abuse were revealed in discrete cell populations by means of the techniques of in situ hybridization histochemistry and in vitro receptor binding and autoradiography. Cocaine subjects had a history of repeated cocaine use and had cocaine and/or cocaine metabolites on board at the time of death. These subjects were compared to control subjects that had both a negative history and toxicology of cocaine use. Selective alterations in mRNA levels of striatal neuropeptides were detected in cocaine subjects compared to control subjects, especially for the opioid peptides. Marked reductions in the levels of enkephalin mRNA and mu opiate receptor binding were found in the caudate and putamen, concomitant with elevations in levels of dynorphin mRNA and kappa opiate receptor binding in the putamen and caudate, respectively. Dopamine uptake site binding was reduced in the caudate and putamen of cocaine subjects. The greater magnitude of changes in the dorsolateral striatum (caudate and putamen) as opposed to the ventromedial striatum (nucleus accumbens) suggests that cocaine abuse preferentially alters the biosynthetic activity of striatal systems associated with sensorimotor functioning. Additionally, an imbalance in the activity of the two major striatal output pathways in cocaine users is implicated because peptide mRNA levels were reduced in enkephalinergic striatopallidal neurons and increased in dynorphinergic striatonigral neurons. Another imbalance, that of reductions of transmitter mRNA and receptor expression associated with euphoria (enkephalin and mu opiate receptors), together with elevations in mRNAs of transmitter systems associated with dysphoria (dynorphin and kappa opiate receptors), suggests a model of dysphoria and craving in the human cocaine addict brain.[147]

In 1995, Gero provides a description of dependence. A theoretical model of drug tolerance and dependence is presented, based on the assumption that, besides their own function, some neurohumors may also modulate the output of other neurohumors. If the receptors of both neurohumors are rapidly desensitized and resensitized by their natural

ligands, but slowly by drugs, prolonged exposure to drugs will necessarily lead to drug tolerance and dependence. This model proposes a function for co-transmitters and, applied to opioid and catecholamine neurohumors and drugs, it explains the presence of enkephalin in sympathetic neurons, the release of catecholamine neurohumors by opiates, the fact that signs of opiate abstinence are largely autonomic symptoms, the attenuation of the opiate abstinence syndrome by alpha2 agonists and its exacerbation by alpha2 antagonists, the analgesic action of excitement, and the increased toxicity of morphine in animals treated with 6-hydroxydopamine. The model also suggests possible interpretations for the late effects of large opiate doses, hyperalgesia caused by very small opiate doses, certain symptoms of autism, and sudden infant death syndrome.[148]

Bibliography

1. Karlson, B.W., M. Hartford, and J. Herlitz, *Treatment of patients with acute myocardial infarction in relation to gender*. *Cardiology*, 1996. **87**(3): p. 230-4.
2. La Harpe, R. and O. Fryc, [*Fatalities associated with methadone administration in the Geneva canton (1987-1993)*]. *Arch Kriminol*, 1995. **196**(1-2): p. 24-9.
3. Ott, P., et al., [*Poisonings due to analgesics during a period of 14 years in Denmark--a registry study of the period 1979-1992*]. *Ugeskr Laeger*, 1995. **157**(7): p. 881-5.
4. Caplehorn, J.R., et al., *Methadone maintenance and addicts' risk of fatal heroin overdose*. *Subst Use Misuse*, 1996. **31**(2): p. 177-96.
5. Reynaud, M., et al., *Six deaths linked to concomitant use of buprenorphine and benzodiazepines*. *Addiction*, 1998. **93**(9): p. 1385-92.
6. Tracqui, A., et al., [*Acute poisoning during substitution therapy based on high-dosage buprenorphine. 29 clinical cases--20 fatal cases*]. *Presse Med*, 1998. **27**(12): p. 557-61.
7. Madadi, P., et al., *Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine*. *Can Fam Physician*, 2007. **53**(1): p. 33-5.
8. Fohr, S.A., *The double effect of pain medication: separating myth from reality*. *J Palliat Med*, 1998. **1**(4): p. 315-28.
9. Field, T.S., et al., *Risk factors for adverse drug events among nursing home residents*. *Arch Intern Med*, 2001. **161**(13): p. 1629-34.
10. Leander, P., L.D. Hove, and P. Ott, [*Who dies of morphine and dextropropoxyphene intoxication? Danish experiences from the period 1979-1992*]. *Ugeskr Laeger*, 1997. **159**(16): p. 2370-4.
11. D'Eramo, E.M., *Mortality and morbidity with outpatient anesthesia: the Massachusetts experience*. *J Oral Maxillofac Surg*, 1999. **57**(5): p. 531-6.

12. Jonasson, U., B. Jonasson, and T. Saldeen, *Correlation between prescription of various dextropropoxyphene preparations and their involvement in fatal poisonings*. Forensic Sci Int, 1999. **103**(2): p. 125-32.
13. Karch, S.B. and B.G. Stephens, *Toxicology and pathology of deaths related to methadone: retrospective review*. West J Med, 2000. **172**(1): p. 11-4.
14. Oderda, G.M., et al., *Cost of opioid-related adverse drug events in surgical patients*. J Pain Symptom Manage, 2003. **25**(3): p. 276-83.
15. Strang, J., et al., *Preventing opiate overdose fatalities with take-home naloxone: pre-launch study of possible impact and acceptability*. Addiction, 1999. **94**(2): p. 199-204.
16. Vilke, G.M., et al., *Are heroin overdose deaths related to patient release after prehospital treatment with naloxone?* Prehosp Emerg Care, 1999. **3**(3): p. 183-6.
17. Kintz, P., *A new series of 13 buprenorphine-related deaths*. Clin Biochem, 2002. **35**(7): p. 513-6.
18. Hankin, C.S., et al., *Adverse events involving intravenous patient-controlled analgesia*. Am J Health Syst Pharm, 2007. **64**(14): p. 1492-9.
19. Digiusto, E., et al., *Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD)*. Addiction, 2004. **99**(4): p. 450-60.
20. Franklin, G.M., et al., *Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002*. Am J Ind Med, 2005. **48**(2): p. 91-9.
21. Gillman, P.K., *Monoamine oxidase inhibitors, opioid analgesics and serotonin toxicity*. Br J Anaesth, 2005. **95**(4): p. 434-41.
22. Good, P.D., P.J. Ravenscroft, and J. Cavenagh, *Effects of opioids and sedatives on survival in an Australian inpatient palliative care population*. Intern Med J, 2005. **35**(9): p. 512-7.
23. Maxwell, J.C., T.W. Pullum, and K. Tannert, *Deaths of clients in methadone treatment in Texas: 1994-2002*. Drug Alcohol Depend, 2005. **78**(1): p. 73-81.
24. Morgan, O., C. Griffiths, and A. Majeed, *Impact of paracetamol pack size restrictions on poisoning from paracetamol in England and Wales: an observational study*. J Public Health (Oxf), 2005. **27**(1): p. 19-24.
25. Rehm, J., et al., *Mortality in heroin-assisted treatment in Switzerland 1994-2000*. Drug Alcohol Depend, 2005. **79**(2): p. 137-43.
26. Wolf, B.C., et al., *One hundred seventy two deaths involving the use of oxycodone in Palm Beach County*. J Forensic Sci, 2005. **50**(1): p. 192-5.
27. Bhananker, S.M., et al., *Injury and liability associated with monitored anesthesia care: a closed claims analysis*. Anesthesiology, 2006. **104**(2): p. 228-34.
28. Chinellato, A., et al., *Retrospective analysis of opioid prescriptions in cancer patients in a northern Italian region*. Br J Clin Pharmacol, 2006. **62**(1): p. 130-3.
29. Coughlin, D.J. and E.P. Krenzlok, *Adverse drug reactions and therapeutic errors in older adults: a hazard factor analysis of poison center data*. Am J Health Syst Pharm, 2006. **63**(22): p. 2228-34.
30. Martin, T.L., K.L. Woodall, and B.A. McLellan, *Fentanyl-related deaths in Ontario, Canada: toxicological findings and circumstances of death in 112 cases (2002-2004)*. J Anal Toxicol, 2006. **30**(8): p. 603-10.

31. Mueller, M.R., N.G. Shah, and M.G. Landen, *Unintentional prescription drug overdose deaths in New Mexico, 1994-2003*. Am J Prev Med, 2006. **30**(5): p. 423-9.
32. Paulozzi, L.J., D.S. Budnitz, and Y. Xi, *Increasing deaths from opioid analgesics in the United States*. Pharmacoepidemiol Drug Saf, 2006. **15**(9): p. 618-27.
33. Lai, S.H., Y.J. Yao, and D.S. Lo, *A survey of buprenorphine related deaths in Singapore*. Forensic Sci Int, 2006. **162**(1-3): p. 80-6.
34. Soyka, M., et al., *One-year mortality rates of patients receiving methadone and buprenorphine maintenance therapy: a nationally representative cohort study in 2694 patients*. J Clin Psychopharmacol, 2006. **26**(6): p. 657-60.
35. Oderda, G.M., et al., *Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay*. Ann Pharmacother, 2007. **41**(3): p. 400-6.
36. Davoli, M., et al., *Risk of fatal overdose during and after specialist drug treatment: the VEdeTTE study, a national multi-site prospective cohort study*. Addiction, 2007. **102**(12): p. 1954-9.
37. Hartung, D.M., et al., *Rates of adverse events of long-acting opioids in a state Medicaid program*. Ann Pharmacother, 2007. **41**(6): p. 921-8.
38. Hull, M.J., et al., *Fatalities associated with fentanyl and co-administered cocaine or opiates*. J Forensic Sci, 2007. **52**(6): p. 1383-8.
39. Tjaderborn, M., et al., *Fatal unintentional intoxications with tramadol during 1995-2005*. Forensic Sci Int, 2007. **173**(2-3): p. 107-11.
40. Wysowski, D.K., *Surveillance of prescription drug-related mortality using death certificate data*. Drug Saf, 2007. **30**(6): p. 533-40.
41. Chugh, S.S., et al., *A community-based evaluation of sudden death associated with therapeutic levels of methadone*. Am J Med, 2008. **121**(1): p. 66-71.
42. Clausen, T., K. Anchersen, and H. Waal, *Mortality prior to, during and after opioid maintenance treatment (OMT): a national prospective cross-registry study*. Drug Alcohol Depend, 2008. **94**(1-3): p. 151-7.
43. Gibson, A., et al., *Exposure to opioid maintenance treatment reduces long-term mortality*. Addiction, 2008. **103**(3): p. 462-8.
44. Watterson, O., D.D. Simpson, and S.B. Sells, *Death rates and causes of death among opioid addicts in community drug treatment programs during 1970-1973*. Am J Drug Alcohol Abuse, 1975. **2**(1): p. 99-111.
45. Velvart, J., J.P. Lorent, and H.R. Gujer, *[Fatal kidney diseases due to analgesic abuse in Switzerland]*. Soz Praventivmed, 1976. **21**(1): p. 25-9.
46. Desmond, D.P., J.F. Maddux, and A. Trevino, *Street heroin potency and deaths from overdose in San Antonio*. Am J Drug Alcohol Abuse, 1978. **5**(1): p. 39-49.
47. Zimney, E.L. and J.L. Luke, *Narcotic-related deaths in the District of Columbia: 1971-1979*. J Forensic Sci, 1981. **26**(3): p. 462-9.
48. Joe, G.W., W. Lehman, and D.D. Simpson, *Addict death rates during a four-year posttreatment follow-up*. Am J Public Health, 1982. **72**(7): p. 703-9.
49. Barr, H.L., et al., *Mortality of treated alcoholics and drug addicts: the benefits of abstinence*. J Stud Alcohol, 1984. **45**(5): p. 440-52.
50. Kringsholm, B., *Deaths among drug addicts in Denmark in 1968-1986*. Forensic Sci Int, 1988. **38**(1-2): p. 139-49.

51. Kringsholm, B., et al., *Deaths among drug addicts in Denmark in 1987-1991*. Forensic Sci Int, 1994. **67**(3): p. 185-95.
52. Haberman, P.W. and G. Natarajan, *Trends in alcoholism and narcotics abuse from medical examiner data*. J Stud Alcohol, 1986. **47**(4): p. 316-21.
53. Wessel, J., [*Circumstances at the time of death in drug fatalities*]. Z Rechtsmed, 1986. **96**(3): p. 215-28.
54. Ellwood, D.A., et al., *Maternal narcotic addiction: pregnancy outcome in patients managed by a specialized drug-dependency antenatal clinic*. Aust N Z J Obstet Gynaecol, 1987. **27**(2): p. 92-8.
55. Costa, C. and N. Vari, [*Etiopathogenetic, clinical and therapeutic findings on infectious endocarditis in drug addicts*]. Clin Ter, 1989. **128**(2): p. 113-21.
56. Graw, M., H.T. Haffner, and K. Besserer, [*Fatalities in drug dependent patients: suicide or accident?*]. Versicherungsmedizin, 1989. **41**(6): p. 188-91.
57. Gronbladh, L. and L. Gunne, *Methadone-assisted rehabilitation of Swedish heroin addicts*. Drug Alcohol Depend, 1989. **24**(1): p. 31-7.
58. Kaa, E., A. Steentoft, and K. Worm, [*Fatal poisoning among narcotic addicts in Denmark in 1984-1985*]. Ugeskr Laeger, 1989. **151**(41): p. 2650-2.
59. Kaa, E. and B. Teige, *Drug-related deaths during the 1980s. A comparative study of drug addict deaths examined at the institutes of forensic medicine in Aarhus, Denmark and Oslo, Norway*. Int J Legal Med, 1993. **106**(1): p. 5-9.
60. Steentoft, A., E. Kaa, and K. Worm, *Fatal intoxications in the age group 15-34 years in Denmark in 1984 and 1985. A forensic study with special reference to drug addicts*. Z Rechtsmed, 1989. **103**(2): p. 93-100.
61. Steentoft, A., et al., *Fatal intoxications in the Nordic countries. A forensic toxicological study with special reference to young drug addicts*. Z Rechtsmed, 1989. **102**(6): p. 355-65.
62. Gronbladh, L., L.S. Ohlund, and L.M. Gunne, *Mortality in heroin addiction: impact of methadone treatment*. Acta Psychiatr Scand, 1990. **82**(3): p. 223-7.
63. Jeanmonod, R. and O. Fryc, [*Toxicomania: death beyond risk. Analysis of cause-of-death in drug addicts*]. Schweiz Med Wochenschr, 1990. **120**(44): p. 1643-8.
64. Kaa, E., [*Narcotic abuse in Jylland. A study based on narcotics and deaths of addicts examined at the Institute of Forensic Medicine, University of Aarhus during the period 1981-1988. 2. Deaths among addicts*]. Ugeskr Laeger, 1990. **152**(15): p. 1080-3.
65. Ott, P., et al., *Consumption, overdose and death from analgesics during a period of over-the-counter availability of paracetamol in Denmark*. J Intern Med, 1990. **227**(6): p. 423-8.
66. Rutenber, A.J., H.D. Kalter, and P. Santinga, *The role of ethanol abuse in the etiology of heroin-related death*. J Forensic Sci, 1990. **35**(4): p. 891-900.
67. Staub, C., R. Jeanmonod, and O. Fryc, *Morphine in postmortem blood: its importance for the diagnosis of deaths associated with opiate addiction*. Int J Legal Med, 1990. **104**(1): p. 39-42.
68. Veljkovic, S., et al., [*Suicide among narcotic addicts*]. Srp Arh Celok Lek, 1990. **118**(5-6): p. 205-7.

69. Delvecchio, G. and V. Brancato, [*Mortality and HIV infection in a group of intravenous heroin addicts from 1985 to 1989*]. *Minerva Med*, 1991. **82**(10): p. 675-8.
70. Walsh, R.A., *Opioid drug accidental deaths in the Newcastle area of New South Wales, 1970-1987*. *Drug Alcohol Rev*, 1991. **10**(1): p. 79-83.
71. Brettel, H.F. and T. Dobbertin, [*Multifactorial studies of 154 fatalities of psychotropic drug poisoning*]. *Beitr Gerichtl Med*, 1992. **50**: p. 127-30.
72. Dukes, P.D., G.M. Robinson, and B.J. Robinson, *Mortality of intravenous drug users: attenders of the Wellington Drug Clinic, 1972-89*. *Drug Alcohol Rev*, 1992. **11**(2): p. 197-201.
73. Davoli, M., et al., *Risk factors for overdose mortality: a case-control study within a cohort of intravenous drug users*. *Int J Epidemiol*, 1993. **22**(2): p. 273-7.
74. Haberman, P.W., J.F. French, and J. Chin, *HIV infection and i.v. drug use: medical examiner cases in Essex and Hudson Counties, New Jersey*. *Am J Drug Alcohol Abuse*, 1993. **19**(3): p. 299-307.
75. Hser, Y.I., D. Anglin, and K. Powers, *A 24-year follow-up of California narcotics addicts*. *Arch Gen Psychiatry*, 1993. **50**(7): p. 577-84.
76. Rodriguez Ortiz de Salazar, B., et al., [*Quality of the certification of death due to acute reaction to opiates and cocaine among inhabitants of the City of Madrid*]. *Rev Sanid Hig Publica (Madr)*, 1993. **67**(5): p. 401-9.
77. Oppenheimer, E., et al., *Death and survival in a cohort of heroin addicts from London clinics: a 22-year follow-up study*. *Addiction*, 1994. **89**(10): p. 1299-308.
78. Chatham, L.R., et al., *Suicidality in a sample of methadone maintenance clients*. *Am J Drug Alcohol Abuse*, 1995. **21**(3): p. 345-61.
79. Kjelsberg, E., M. Winther, and A.A. Dahl, *Overdose deaths in young substance abusers: accidents or hidden suicides?* *Acta Psychiatr Scand*, 1995. **91**(4): p. 236-42.
80. Rossow, I. and K.B. Kielland, [*Mortality among drug addicts in Norway*]. *Tidsskr Nor Laegeforen*, 1995. **115**(9): p. 1050-4.
81. Ghodse, H., A. Oyefeso, and B. Kilpatrick, *Mortality of drug addicts in the United Kingdom 1967-1993*. *Int J Epidemiol*, 1998. **27**(3): p. 473-8.
82. Hall, W. and S. Darke, *Trends in opiate overdose deaths in Australia 1979-1995*. *Drug Alcohol Depend*, 1998. **52**(1): p. 71-7.
83. Sorensen, H.J., et al., *Drug-use pattern, comorbid psychosis and mortality in people with a history of opioid addiction*. *Acta Psychiatr Scand*, 2005. **111**(3): p. 244-9.
84. Bargagli, A.M., et al., *Drug-related mortality and its impact on adult mortality in eight European countries*. *Eur J Public Health*, 2006. **16**(2): p. 198-202.
85. Jauncey, M.E., L.K. Taylor, and L.J. Degenhardt, *The definition of opioid-related deaths in Australia: implications for surveillance and policy*. *Drug Alcohol Rev*, 2005. **24**(5): p. 401-9.
86. Darke, S., S. Kaye, and J. Duflo, *Systemic disease among cases of fatal opioid toxicity*. *Addiction*, 2006. **101**(9): p. 1299-305.
87. Geber, W.F. and L.C. Schramm, *Congenital malformations of the central nervous system produced by narcotic analgesics in the hamster*. *Am J Obstet Gynecol*, 1975. **123**(7): p. 705-13.

88. Lichtblau, L. and S.B. Sparber, *Opiate withdrawal in utero increases neonatal morbidity in the rat*. Science, 1981. **212**(4497): p. 943-5.
89. Stauber, M., M. Schwerdt, and B. Hollenbach, [*Pregnancy, labour, and puerperium in heroin addicted women, with reference to experience and the present state of knowledge (author's transl)*]. Geburtshilfe Frauenheilkd, 1982. **42**(5): p. 345-52.
90. Finnegan, L.P., *Effects of maternal opiate abuse on the newborn*. Fed Proc, 1985. **44**(7): p. 2314-7.
91. Ramabadran, K. and M. Bansinath, *Opioid peptides from milk as a possible cause of sudden infant death syndrome*. Med Hypotheses, 1988. **27**(3): p. 181-7.
92. Lam, S.K., et al., *Narcotic addiction in pregnancy with adverse maternal and perinatal outcome*. Aust N Z J Obstet Gynaecol, 1992. **32**(3): p. 216-21.
93. Hanssler, L. and C. Roll, [*Increased thrombocyte count in newborn infants of drug-dependent mothers*]. Klin Padiatr, 1994. **206**(1): p. 55-8.
94. Ostrea, E.M., Jr., A.R. Ostrea, and P.M. Simpson, *Mortality within the first 2 years in infants exposed to cocaine, opiate, or cannabinoid during gestation*. Pediatrics, 1997. **100**(1): p. 79-83.
95. Partridge, J.C. and S.N. Wall, *Analgesia for dying infants whose life support is withdrawn or withheld*. Pediatrics, 1997. **99**(1): p. 76-9.
96. Dashe, J.S., et al., *Opioid detoxification in pregnancy*. Obstet Gynecol, 1998. **92**(5): p. 854-8.
97. Hall, R.W., et al., *Morphine, hypotension, and adverse outcomes among preterm neonates: who's to blame? Secondary results from the NEOPAIN trial*. Pediatrics, 2005. **115**(5): p. 1351-9.
98. Fajemirokun-Odudeyi, O., et al., *Pregnancy outcome in women who use opiates*. Eur J Obstet Gynecol Reprod Biol, 2006. **126**(2): p. 170-5.
99. Kahlert, C., C. Rudin, and C. Kind, *Sudden infant death syndrome in infants born to HIV-infected and opiate-using mothers*. Arch Dis Child, 2007. **92**(11): p. 1005-8.
100. Binder, T. and B. Vavrinkova, *Prospective randomised comparative study of the effect of buprenorphine, methadone and heroin on the course of pregnancy, birthweight of newborns, early postpartum adaptation and course of the neonatal abstinence syndrome (NAS) in women followed up in the outpatient department*. Neuro Endocrinol Lett, 2008. **29**(1): p. 80-6.
101. Twycross, R.G., *Diseases of the central nervous system. Relief of terminal pain*. Br Med J, 1975. **4**(5990): p. 212-4.
102. Olesen, J., et al., [*Medicinal pain treatment in cancer and terminal conditions: nearly everyone can be maintained painfree until a few days before death*]. Sygeplejersken, 1979. **79**(43): p. 4-8.
103. Noyes, R., Jr., *Treatment of cancer pain*. Psychosom Med, 1981. **43**(1): p. 57-70.
104. McGivney, W.T. and G.M. Crooks, *The care of patients with severe chronic pain in terminal illness*. Jama, 1984. **251**(9): p. 1182-8.
105. Goldberg, R.J., et al., *Analgesic use in terminal cancer patients: report from the National Hospice Study*. J Chronic Dis, 1986. **39**(1): p. 37-45.
106. Motsch, J., et al., [*Continuous intrathecal opiate therapy with a portable drug pump in cancer pain*]. Anasth Intensivther Notfallmed, 1988. **23**(5): p. 271-5.

107. Creagan, E.T. and J.M. Wilkinson, *Pain relief in terminally ill patients*. Am Fam Physician, 1989. **40**(6): p. 133-40.
108. Tsuneto, S. and T. Kashiwagi, [*Pain control in terminal cancer*]. Gan To Kagaku Ryoho, 1989. **16**(4 Pt 1): p. 759-66.
109. Bonifant, J.D. and M. Clark-Reynolds, *Morphine sulphate tablets in hospice practice*. Postgrad Med J, 1991. **67 Suppl 2**: p. S74-8.
110. Dixon, P. and I. Higginson, *AIDS and cancer pain treated with slow release morphine*. Postgrad Med J, 1991. **67 Suppl 2**: p. S92-4.
111. Ekeberg, O., O. Ellingsen, and D. Jacobsen, *Suicide and other causes of death in a five-year follow-up of patients treated for self-poisoning in Oslo*. Acta Psychiatr Scand, 1991. **83**(6): p. 432-7.
112. Filseth, O.M., et al., [*Opiate-related deaths among drug addicts. Autopsy findings, circumstances and forensic toxicologic analyses regarding deaths*]. Tidsskr Nor Laegeforen, 1991. **111**(13): p. 1629-32.
113. Brescia, F.J., et al., *Pain, opioid use, and survival in hospitalized patients with advanced cancer*. J Clin Oncol, 1992. **10**(1): p. 149-55.
114. Mercadante, S., *Celiac plexus block versus analgesics in pancreatic cancer pain*. Pain, 1993. **52**(2): p. 187-92.
115. Crane, R.A., *Intermittent subcutaneous infusion of opioids in hospice home care: an effective, economical, manageable option*. Am J Hosp Palliat Care, 1994. **11**(1): p. 8-12.
116. Mercadante, S., M. Armata, and L. Salvaggio, *Pain characteristics of advanced lung cancer patients referred to a palliative care service*. Pain, 1994. **59**(1): p. 141-5.
117. Siever, B.A., *Pain management and potentially life-shortening analgesia in the terminally ill child: the ethical implications for pediatric nurses*. J Pediatr Nurs, 1994. **9**(5): p. 307-12.
118. Cherny, N.J., et al., *Opioid pharmacotherapy in the management of cancer pain: a survey of strategies used by pain physicians for the selection of analgesic drugs and routes of administration*. Cancer, 1995. **76**(7): p. 1283-93.
119. Gavrin, J. and C.R. Chapman, *Clinical management of dying patients*. West J Med, 1995. **163**(3): p. 268-77.
120. Zech, D.F., et al., *Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study*. Pain, 1995. **63**(1): p. 65-76.
121. Butler, R.N., et al., *A peaceful death: how to manage pain and provide quality care. A roundtable discussion: Part 2*. Geriatrics, 1996. **51**(6): p. 32-5, 39-40, 42.
122. Cavanaugh, T.A., *The ethics of death-hastening or death-causing palliative analgesic administration to the terminally ill*. J Pain Symptom Manage, 1996. **12**(4): p. 248-54.
123. Hawryluck, L.A. and W.R. Harvey, *Analgesia, virtue, and the principle of double effect*. J Palliat Care, 2000. **16 Suppl**: p. S24-30.
124. Folker, A.P., et al., *Experiences and attitudes towards end-of-life decisions amongst Danish physicians*. Bioethics, 1996. **10**(3): p. 233-49.
125. Meuret, G. and H. Jocham, *Patient-controlled analgesia (PCA) in the domiciliary care of tumour patients*. Cancer Treat Rev, 1996. **22 Suppl A**: p. 137-40.

126. Mercadante, S., et al., *Monitoring of opioid therapy in advanced cancer pain patients*. J Pain Symptom Manage, 1997. **13**(4): p. 204-12.
127. Cooke, M., et al., *Informal caregivers and the intention to hasten AIDS-related death*. Arch Intern Med, 1998. **158**(1): p. 69-75.
128. Guest, J.F., W.M. Hart, and R.F. Cookson, *Cost analysis of palliative care for terminally ill cancer patients in the UK after switching from weak to strong opioids*. Palliative Care Advisory Committee. Pharmacoeconomics, 1998. **14**(3): p. 285-97.
129. Mercadante, S., et al., *Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home*. J Clin Oncol, 1998. **16**(11): p. 3656-61.
130. Mercadante, S., et al., *Dextropropoxyphene versus morphine in opioid-naive cancer patients with pain*. J Pain Symptom Manage, 1998. **15**(2): p. 76-81.
131. Morita, T., et al., *A prospective study on the dying process in terminally ill cancer patients*. Am J Hosp Palliat Care, 1998. **15**(4): p. 217-22.
132. Daeninck, P.J. and E. Bruera, *Opioid use in cancer pain. Is a more liberal approach enhancing toxicity?* Acta Anaesthesiol Scand, 1999. **43**(9): p. 924-38.
133. Rocker, G.M., et al., *Most critically ill patients are perceived to die in comfort during withdrawal of life support: a Canadian multicentre study*. Can J Anaesth, 2004. **51**(6): p. 623-30.
134. Chau, T.T. and L.S. Harris, *Comparative studies of the pharmacological effects of the d- and l-isomers of codeine*. J Pharmacol Exp Ther, 1980. **215**(3): p. 668-72.
135. Pasternak, G.W., S.R. Childers, and S.H. Snyder, *Opiate analgesia: evidence for mediation by a subpopulation of opiate receptors*. Science, 1980. **208**(4443): p. 514-6.
136. Coleman, S.B., *Incomplete mourning and addict/family transactions: a theory for understanding heroin abuse*. NIDA Res Monogr, 1980. **30**: p. 83-9.
137. Rounsaville, B.J., et al., *Pathways to opiate addiction: an evaluation of differing antecedents*. Br J Psychiatry, 1982. **141**: p. 437-46.
138. Pare, E.M., J.R. Monforte, and R.J. Thibert, *Morphine concentrations in brain tissue from heroin-associated deaths*. J Anal Toxicol, 1984. **8**(5): p. 213-6.
139. Rajs, J., T. Harm, and K. Ormstad, *Postmortem findings of pulmonary lesions of older datum in intravenous drug addicts. A forensic-pathologic study*. Virchows Arch A Pathol Anat Histopathol, 1984. **402**(4): p. 405-14.
140. Poling, A., et al., *Lethality of opioid and antihistaminic combinations in mice*. Pharmacol Biochem Behav, 1985. **22**(2): p. 333-5.
141. Edwards, J.G. and A. Goldie, *A ten-year follow-up study of Southampton opiate addicts*. Br J Psychiatry, 1987. **151**: p. 679-83.
142. Hall, R.I., et al., *Dezocine-MAC reduction and evidence for myocardial depression in the presence of enflurane*. Anesth Analg, 1987. **66**(11): p. 1169-74.
143. Buchanan, J.F. and C.R. Brown, *'Designer drugs'. A problem in clinical toxicology*. Med Toxicol Adverse Drug Exp, 1988. **3**(1): p. 1-17.
144. Jacobson, B., et al., *Opiate addiction in adult offspring through possible imprinting after obstetric treatment*. Bmj, 1990. **301**(6760): p. 1067-70.
145. Hauser, K.F. and A. Stiene-Martin, *Characterization of opioid-dependent glial development in dissociated and organotypic cultures of mouse central nervous*

- system: critical periods and target specificity.* Brain Res Dev Brain Res, 1991. **62**(2): p. 245-55.
146. Maneckjee, R. and J.D. Minna, *Nonconventional opioid binding sites mediate growth inhibitory effects of methadone on human lung cancer cells.* Proc Natl Acad Sci U S A, 1992. **89**(4): p. 1169-73.
147. Hurd, Y.L. and M. Herkenham, *Molecular alterations in the neostriatum of human cocaine addicts.* Synapse, 1993. **13**(4): p. 357-69.
148. Gero, A., *Desensitization and neurohumor modulation: a model of drug dependence II.* J Theor Biol, 1995. **177**(4): p. 357-68.