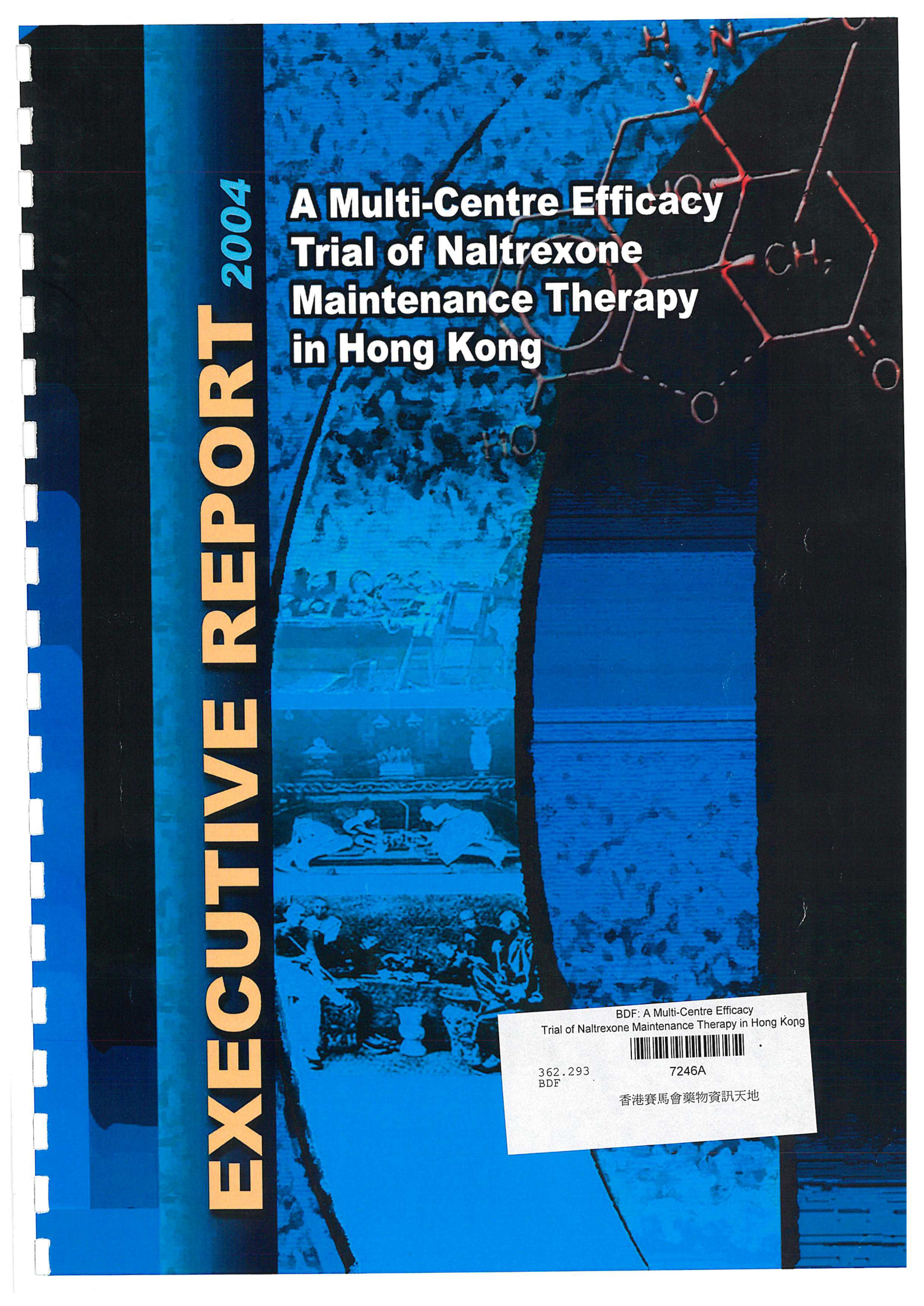
EXECUTIVE REPORT 2004

A Multi-Centre Efficacy Trial of Naltrexone Maintenance Therapy in Hong Kong



EXECUTIVE REPORT

A Multi-Centre Efficacy Trial of Naltrexone Maintenance Therapy in Hong Kong

Contents

Chapter 1. Study Background

1.1 History of Naltrexone Use in Medicine

1.1.1 Overview of Methadone Treatment Programme Review

The Working Group of the Methadone Treatment Programme Review recommended to conduct more research in Hong Kong to assess the effectiveness of naltrexone treatment in relapse prevention.

1.1.1.1 Hong Kong adopts a multi-modality approach in providing drug treatment and rehabilitation services for drug dependent persons with different needs from various backgrounds[1]. Amongst a variety of treatment modalities, the Methadone Treatment Programme (MTP), which was launched in Hong Kong in 1972, is the sole substitution treatment model for opiate dependent patients.

1.1.1.2 Since the commencement of MTP in Hong Kong in 1970s, the Government has kept the effectiveness of the programme under review and monitoring. Nevertheless, there has long been controversy surrounding this treatment modality. Specifically, methadone is alleged as "another addictive drug that substitutes

[1] This included compulsory placement scheme by the Correctional Services Department, voluntary residential treatment programme operated by non-governmental organisations, Methadone Clinics of the Department of Health, Substance Abuse Clinics of the Hospital Authority, rehabilitation services provided by non-governmental agencies that offered a variety of services including counselling, case-finding, drug treatment, and crisis interventions etc.

heroin". In addition to the emergence of new drugs that purported to serve as a substitute of methadone, the Action Committee Against Narcotics (ACAN) Sub-committee on Treatment and Rehabilitation decided that a comprehensive review of the MTP should be conducted to evaluate the MTP in current circumstances, as well as assessing whether there were alternative medications to methadone in detoxification and maintenance. A Working Group was thus formed to conduct the review in May 1999.

1.1.1.3 The Working Group completed the MTP Review in 2000 and raised a number of recommendations. Overall speaking, the Group concluded that the existing MTP fulfilled its declared objectives and recommended continuation of the service though there were areas for change and improvement, including support services, referral services, and physical setting etc. Regarding the alternative medications to methadone, the Working Group proposed a recommendation to carry out more research to fully assess the effectiveness of naltrexone in relapse prevention of detoxified patients, with reference to the experience of naltrexone use in Singapore and the Castle Peak Hospital.

1.1.1.3.1 Naltrexone Use in Singapore

1.1.1.3.1.1 The service modality of naltrexone treatment in Singapore was outlined in the MTP review. Since June 1995, naltrexone was incorporated into the Halfway House Scheme and the

Residential Scheme under the mainstream Community-Based Rehabilitative programmes.

1.1.1.3.1.2 In practical operation, detoxified drug addicts on naltrexone treatment are managed in an outpatient setting, which requires patients to attend designated centres thrice a year for drug dispensing. Medical consultation and counselling services are provided upon request. The naltrexone treatment is also available at private clinics and government polyclinics, which increases the number of avenues for those in need of the treatment.

1.1.1.3.2 Naltrexone Use in the Castle Peak Hospital

1.1.1.3.2.1 The Castle Peak Hospital (CPH) initiated the naltrexone treatment programme since May 1996. The recruited subjects were completely detoxified patients who were motivated and able to involve a significant figure to supervise the ingestion of naltrexone. A total of 24 subjects were enrolled from 1 May 1996 to 31 March 1999. The outcome assessment was made in the period from 11 October 1999 to 15 November 1999.

1.1.1.3.2.2 Only 8 of the 24 subjects had maintenance period of 30 days or more (33%). Of these 8 subjects, only 4 had completed the maintenance treatment of 90 days. The dropout rate was 83%.

1.1.1.3.2.3 Of the 4 cases that remained in the naltrexone treatment for 90 days or more, 3 were still abstinent at the outcome assessment. The successful abstinent rate is 75%, which is higher than the group's overall abstinent rate of 41%. The Working Group commented that this appeared to confirm the consensus agreement that those willing to maintain on naltrexone for three months or more generally do well. However, factors contributing to the success rate remained unknown.

1.1.1.3.2.4 The Working Group noted that it was difficult to draw any meaningful conclusion from the naltrexone study of CPH with such a small sample. Nevertheless, given the preliminary data so far presented, the Working Group was of the view that only patients with high motivation and family support were suitable for using naltrexone should the medication be widely applied in Hong Kong.

1.1.1.4 Having regard to the experience of using naltrexone in the local hospital and overseas countries, the Working Group suggested conducting more research on naltrexone as a supplementary treatment in Hong Kong. With the involvement of the Substance Abuse Clinics (SACs) of the Hospital Authority and interested drug treatment and rehabilitation agencies, the study would aim at evaluating the effectiveness of naltrexone treatment in relapse prevention to detoxified opiate addicts in a territory-wide scale.

1.2 Supports of Beat Drugs Fund and the Monitoring Group

1.2.1 In view of the past experience in the use of naltrexone, together with the available scientific evidence, our research team submitted a study proposal for the application of the Beat Drugs Fund in pursuant to the recommendation of the Working Group of the MTP Review. The application was approved in April 2002.

1.2.2 A Monitoring Group (MG) was formed to monitor the project and to advise the research team in July 2002. The MG comprised of experts from the Chinese University of Hong Kong, the Hospital Authority, Department of Health and Narcotics Division.

1.3 Objectives

1.3.1 The objectives of the study are:

1) to study the efficacy of naltrexone maintenance in preventing relapse among recently detoxified heroin addicts in Hong Kong; and

2) to examine the cost and policy implications of implementing naltrexone maintenance programme in Hong Kong.

Chapter 2. Technical Background and Literature Review

2.1 Technical Background of Naltrexone

2.1.1 Mechanism of Action

Naltrexone is a competitive opioid antagonist that provides blockade action to exogenous opioids. It is non-addictive and long acting.

2.1.1.1 Addiction, in the simplest term, is the conditioning of an individual to desire the euphoria that the addictive substance produces, and to not desire the pain that followed lack of the substance. Thus, according to Wikler's well-known theory, the development of drug dependence may be defined in terms of operant conditioning; and the use of opioids depends on both positive and negative reinforcements that provide a strong incentive for continued opioid abuse.

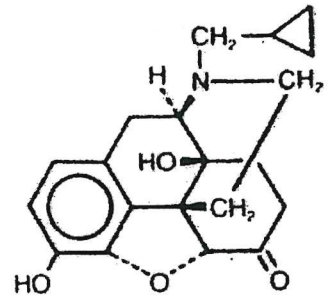
2.1.1.2 The treatment of addiction with opioid antagonists (e.g. naltrexone), therefore, aims at the extinction of drug-seeking behaviour by blocking the reinforcement produced by the self-administration of opioids. In this way, continued drug abuse may eventually be extinguished. Extinction also depends on the weakening of the conditioned abstinence syndrome, i.e. a complex conditioned responses produced by various environmental cues or stimuli that have been previously paired with drug effects when the

patient was still using opioids.

2.1.2 Clinical Pharmacology

2.1.2.1 The following information, which elucidates the pharmacological aspect of naltrexone, is sourced from the product monogram of naltrexone (TREXAN), manufactured by the pharmaceutical company Du Pont.

2.1.2.2 **Chemical Description:** Naltrexone/ naltrexone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone, and is technically, therefore, a thebaine derivative. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group.



naltrexone hydrochloride

2.1.2.3 Pharmacological Properties

2.1.2.3.1 Naltrexone is indicated to provide blockage of the pharmacological effects of exogenously administered opioids as an adjunct of the maintenance of the opioid free state in detoxified formerly opioid-independent individuals.

2.1.2.3.2 It is a pure opioid antagonist that markedly attenuates or completely blocks, reversibly, the subjective effects of

intravenously administered opioids.

2.1.2.3.3 Naltrexone has no opioid agonist properties. Its administration is not associated with the development of tolerance or dependence.

2.1.2.3.4 Clinical studies indicate that 50 mg of naltrexone will block the pharmacological effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that doubling the dose of naltrexone provides blockade for 48 hours, and tripling the dose of naltrexone provides blockade for about 72 hours.

2.1.2.3.5 While the mechanism of action is not fully understood, the preponderance of evidence suggests that naltrexone blocks the effects of opioids by competitive binding at opioid receptors. This makes the blockade produced potentially surmountable.

2.1.2.4 Adverse Effects

2.1.2.4.1 While extensive clinical studies evaluating the use of naltrexone in detoxified formerly opioid dependent individuals failed to identify any single, serious untoward risk of naltrexone use, placebo controlled studies employing up to five-fold higher doses of naltrexone (up to 300 mg per day) than that recommended for use in opiate receptor blockade have shown that naltrexone causes hepatocellular injury in a substantial proportion of patients

exposed at this higher dose.

2.1.2.4.2 Other than hepatocellular injury reported during clinical testing, the following adverse reactions have been reported both at baseline and during the naltrexone medication period at an incidence rate of more than 10%: Difficulty in sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache. Loss of appetite, diarrhoea, constipation, increased thirst, increased energy, feeling down, irritability skin rash, dizziness etc., were reported at an incidence rate of less than 10%. Yet, except liver test abnormalities, results of laboratory tests have not shown consistent patterns of abnormalities that can be attributed to treatment with naltrexone.

2.1.2.4.3 In summary, among opioid free individuals, naltrexone administration at the recommended dose has not been associated with a predictable profile of serious adverse or untoward events.

2.1.2.5 Contradictions and Precautions

2.1.2.5.1 Naltrexone is contradicted in: 1) patients receiving opioid analgesics; 2) opioid dependent patients; 3) patients in acute opioid withdrawal; 4) any individual who has failed to pass the naloxone challenge test; 5) any individual who has a positive urine screen for opioids; 6) any individual with a history of sensitivity to

naltrexone; 7) any individual with acute hepatitis or liver failure.

2.1.2.5.2 It should be cautious that in subjects physically dependent on opioids, naltrexone would precipitate withdrawal symptomatology. To prevent occurrence of an acute abstinence syndrome, or exacerbation of a pre-existing sub-clinical abstinence syndrome, patients should remain opioid free for a minimum of 7-10 days before starting naltrexone.

2.1.2.5.3 Since the absence of an opioid drug in the urine is often not a sufficient proof that a patient is opioid free, a naloxone challenge test, taken by either intravenous or subcutaneous route, should be employed to exclude the possibility of precipitating a withdrawal reaction following administration of naltrexone. Naloxone hydrochloride (NARCAN) could briefly block the opiate receptors in the body and cause withdrawal symptoms in those who are opiate dependent. In any case there are elicitations of withdrawal signs and symptoms observed in participants during a specific post-challenge observation period, which indicates the presence of potential risk, naltrexone should not be administered. The side effects are similar to opiate withdrawal symptoms, though rare, and would be interpreted as test failure if the effects were significantly present. Hence, participants must be closely monitored to identify any vital signs change and emergence of withdrawal symptoms after the naloxone challenge test is

administered. The administration details of naloxone challenge test, including purpose, procedures, precautions etc., should be explained to the study participants in advance. Written informed consent to the naloxone challenge test would also be obtained upon participant's agreement of administration.

2.1.2.5.4 Since the blockade effect produced by naltrexone is surmountable, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous, and may lead to a fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering a life-endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse).

2.1.2.5.5 Since naltrexone has the capacity to cause dose related hepatocellular injury, physicians should establish whether the patients has subclinical liver injury or disease prior to making a decision to initiate treatment in naltrexone.

2.2 Scientific Evidence of Naltrexone Maintenance

Efficacy of naltrexone in maintenance treatment has been reported in several overseas and Chinese studies. The surmountable properties of naltrexone warrant our special attention to the potential risk associated with the use of naltrexone.

2.2.1 The research team has carried out a thorough literature review to examine issues related to the use of naltrexone in maintenance therapy. Studies of naltrexone maintenance treatment overseas and in Mainland China, as well as the corresponding unfavourable issues were briefly summarized in the following paragraphs. The overseas [**Appendix I**] and Chinese [**Appendix II**] studies of naltrexone were listed in the appendices.

2.2.2 Studies of Naltrexone Treatment Overseas

2.2.2.1 Since 1973, naltrexone has been used experimentally in the maintenance treatment of opioid dependence, mostly in combination with other drugs (e.g. clonidine) or other therapies. It was until mid 1980's that naltrexone was widely used in maintenance therapy in many countries (e.g., USA since 1984; UK since 1988; Australia since 1999). In spite of its extensive use, only a few high-standard documentation of research studies assessing

the efficacy of naltrexone on opioid dependence have been published.

2.2.2.2 Amongst the limited number of research studies on naltrexone use, its efficacy as maintenance medication in heroin dependence was supported by several double blind controlled studies in the U.S. and Europe (Mello et al., 1981). These studies suggested that naltrexone could reduce the risk of relapse, as well as the number of drug using days. Cornish et al (1977) reported significantly lower rates of opioid-positive urine specimens and re-incarcerations for the naltrexone group. The retention rate was better but not significant. In another study, Hollister et al (1978) showed that the naltrexone treated group had slightly better opiate-free urine tests and treatment retention. Similar findings were also reported by Ladewig (1990) and Rawson et al (1979).

2.2.2.3 These studies also pointed out that individuals with family supervision and rehabilitative treatment were most likely to benefit from naltrexone maintenance (Hulse et al., 2000). Carroll et al (2001) further addressed that behavioural therapies could be used to address the weakness of specific pharmacotherapies such as non-compliance, thus playing a substantial role in broadening the utility of available pharmacotherapies.

2.2.2.4 It is noteworthy that only a limited number of clinical controlled trials had been conducted to assess the efficacy of naltrexone. It is the result of general difficulties to do blinding and randomization for trials of naltrexone treatment. Some investigators maintained that naltrexone treatment was almost impossible to be blinded as patients could test the medication easily by injecting heroin (Kirchmayer et al, 2004). As a consequence, it would be doubtful for patients who found they were not receiving naltrexone to stay in the study. Further, Keegan et al (1976) pointed out that there were some attritions when patients were informed that they might not receive naltrexone. The informed consent, which made clear all the possible risks to be encountered, might also cause a tendency to limit participation.

2.2.3 Studies of Naltrexone Treatment in China

2.2.3.1 In Mainland China, naltrexone was applied in maintenance therapy since mid 1990's. A wide variety of treatment modalities with naltrexone had been implemented at various drug treatment centres throughout the country. To evaluate the outcome and effectiveness of naltrexone treatment, a number of studies were carried out in recent years. The majority of these studies were uncontrolled or compared with the retrospective data of individual participant.

2.2.3.2 A number of open and retrospective studies on naltrexone

maintenance treatment were conducted in China. The results of these studies showed that 1) the retention rate of naltrexone treatment ranged from 24-58% [姜佐寧等(1998); 蔣忠亮(1999); 王文甫(2001)]; 2) the abstinence rate ranged approximately from 25%-50% [楊曉松等(1998); 蘇木金等(2001b); 楊征等(1999)] and some studies reported a significant reduction in relapse rate when compared with retrospective self-control data [姜佐寧等(1999); 劉運琴等(2003);張志祥等(2002)]; 3) a significant reductions in craving level is also reported during the treatment [蘇木金等(2001a); 劉運琴等(2003)]; and 4) naltrexone only caused mild side effects in Chinese addicts and the adverse reactions declined during the treatment [靳方等(2002); 姜佐寧等(1998)].

2.2.3.3 Despite the uncontrolled and retrospective studies, only a handful of controlled clinical trials were conducted in China. In a recent study that employed both double blind and open trial design (Guo et al., 2001), 49 participants were recruited in the double-blind study. The treatment outcomes had shown that a significantly longer abstinence period and a lower percentage of positive urine test was found in the naltrexone-treated group than in the placebo group. The authors of this study suggested that naltrexone was effective in relapse prevention with only mild side effects in the

Chinese population.

2.2.3.4 Generally speaking, the naltrexone studies conducted in Mainland China showed an inclination of positive outcomes for those patients maintained on naltrexone. Nonetheless, since most of the studies were uncontrolled and retrospective in nature, extra cautions should be paid to the analysis of the results of these studies. It would be arbitrary to determine whether the reported outcomes of the uncontrolled studies were due to naltrexone or other parameters. Retrospective data is also less desirable as it would be difficult to control the veracity of the recalled information.

2.2.4 Unfavourable Aspects of Naltrexone Use

2.2.4.1 Alongside the positive findings reported in the MTP review and several clinical studies, careful investigations have been done to examine the less favourable side of naltrexone use. The greatest risk associated with naltrexone treatment is heroin overdose in patients who use opioid while being treated with naltrexone. A number of mortality related to the use of naltrexone were reported in the literature (Miotto et al, 1997; Ritter, 2002; Arnold-Reed, 2003; Digiusto et al, 2004).

2.2.4.2 In Australia, there was a growth in the prevalence of opioid dependence, leading to an increasing interest in using naltrexone during the 1990's. A number of medical practitioners began using

the Special Access Scheme (which under certain circumstances allows the prescribing of unregistered drugs) to use naltrexone. Results of the first Australian clinical trial of naltrexone in the management of opioid dependence were published in 1998. In 1999, the drug was registered for use in Australia (Bell et al, 2003).

2.2.4.3 Followed by the widespread use of naltrexone, alarming rates of overdose and suicide among patients receiving naltrexone treatment had been revealed by the Australian media [**Appendix III**]. The study report mentioned in the news article (National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD): Report of Results and Recommendations) was released by the National Drug and Alcohol Research Centre in July 2001. The findings stated that naltrexone maintenance treatment was associated with a significant higher (non-fatal and fatal) heroin overdose rate compared with methadone, buprenorphine and LAAM. A trend towards a higher death rate (4 deaths among 454 patients) associated with naltrexone treatment was also reported, though the difference was not statistically significance. A recent longitudinal study, based on the data set included in the NEPOD project, also reported that naltrexone participants were 7.6 times more likely than agonist participants to experience an overdose after existing treatment (Digiusto et al., 2004).

2.2.4.4 A number of studies were carried out to investigate the linkage

between overdose, mood disorders and naltrexone use. For instance, in a US study evaluating naltrexone with either an intensive psychological protocol or standard community treatment for opioid dependence (Miotto et al, 1997), 13 of 81 subjects overdosed within a 12-month period of study participation. There were 4 fatalities, one of which was a suicide. Among the 9 nonfatal overdoses, there were 4 suicide attempts. In view of a possible association between naltrexone and mood disorders, the research team later reviewed pharmacological and clinical data in alcohol, opioid and nicotine studies to determine if an association between naltrexone and dysphoria exists (Miotto et al, 2002). These studies could not conclude dysphoria to be a serious side effect produced by naltrexone treatment.

2.2.4.5 In another study by Ritter (2002), the relationship between naltrexone, depression and risk of overdose was examined. Research to date demonstrates that the addition of naltrexone does not necessarily increase depression in patients. However, it was found that the risk of non-fatal heroin overdose was significantly elevated after naltrexone treatment as a result of reduced tolerance. Equivocal findings showed that the mortality rate subsequent to naltrexone treatment appeared to be equivalent to or greater than that for untreated heroin users.

2.2.4.6 Although the linkage between naltrexone use and mood disorders has not been proved with strong scientific evidence, the controversies reported to date, together with a number of deaths overseas, implied an ambivalent position of the merits of naltrexone treatment that deserved our in-depth scientific investigations.

2.2.5 Cochrane Review of Naltrexone Maintenance Treatment for Opioid Dependence

2.2.5.1 Against the absence of comprehensive review and meta-analysis of the clinical trials on naltrexone, an evidence-based systematic review, Cochrane Review, examined the efficacy of naltrexone maintenance treatment since 1999. The review design was in accordance with the methodology developed by the Cochrane Collaborations based on either randomized controlled trial (RCT) or controlled clinical trial (CCT). Cochrane Review is a highly regarded source of evidence about the effects of healthcare intervention, which contributes to its strength of systematic approach to review scientific evidence in response to comments, criticism and any recent information available.

2.2.5.2 The objective of the review study was to evaluate the efficacy of maintenance treatment of heroin dependence after detoxification, comparing naltrexone with placebo or other pharmacological or behavioural treatments. Reviewers evaluated data independently

and analysed outcome measures taking into consideration adherence to and success of the study intervention. Where possible, meta-analysis was performed (Kirchmayer et al., 2004).

2.2.5.3 Since the beginning of naltrexone use in 1970's, 11 studies met the criteria for inclusion in this review. The main result of the systematic review was that there was no sufficient evidence to evaluate the efficacy of naltrexone treatment on opioid dependence. A significant reduction of re-incarcerations was found for patients treated with naltrexone and behaviour therapy in respect to those treated with behaviour therapy only. The other outcomes considered in the meta-analysis, including the successful completion of treatment and the use of opioids under treatment comparing naltrexone vs. placebo did not yield any significant results. Nevertheless, reviewers criticized that the methodological quality of the included studies varied and was generally poor. Meta-analysis could be performed to a very low degree, since the outcome measures were rather heterogeneous.

2.2.5.4 Difficulties encountered in conducting clinical trials were discussed in the review. Reviewers pointed out that features of the study population, drug addicts, which were characterized by low motivation, high dropout rates and unreliability, might partly explain the general hurdles of a successful clinical trial. These inevitably made study adherence and a long-term follow up

extremely difficult. A high rate of dropout, which obviously was selective, led to a very low percentage of study completion (e.g. Curran, 1976: 10.5%), and the high rate of early dropouts produced unintended bias towards those patients best motivated. Therefore, given that selective dropout seems to be hardly avoidable, Shufman et al. (1994) regarded the comparability of naltrexone and placebo groups as limited.

2.2.5.5 Furthermore, randomization is difficult to be done in the case of antagonist treatment. As experienced by Grey (1986), naltrexone treatment in general could not be blinded, as the participants could easily distinguish between naltrexone and placebo by injecting heroin. Even in a study in which blinding is done, drop-out in the placebo group was much higher than that of the naltrexone group, since many patients distinguished the more bitter taste of the active medicine despite elaborate dilutions (Taintor et al., 1975). To overcome all these difficulties, investigators could only resort to different administration methods to ensure the trial completion rate, but the wide variety of individually designed studies made meta-analysis almost impossible.

2.2.5.6 In conclusion, reviewers commented that final conclusions on whether naltrexone treatment was effective in maintenance therapy could not be drawn from the clinical trials available so far. Further studies were needed before making a clear decision on

whether to keep on using and even enlarge its use as far as possible, or come to a halt and concentrate on other alternatives. A trend in favour of treatment with naltrexone was observed for certain target groups, particularly those who were highly motivated.

- **The evidence-based systematic review on naltrexone maintenance treatment, Cochrane Review, concluded that empirical evidence on the effectiveness of naltrexone in maintenance therapy is inconclusive. Further studies are needed for a clear decision.**

Chapter 3. Design and Methodology of Study

3.1 The Randomised Controlled Trial

3.1.1 The Monitoring Group (MG) discussed the research design at its 1st meeting held in August 2002. At the meeting, the MG raised the importance of a control group for comparison and requested the research team to consider a study design with a control comparison. After deliberation and consultation with the subject officer of Hospital Authority, the research team drew up a study protocol of a double-blind randomised controlled trial (RCT).

3.1.2 In a standard double blind RCT study, participants in the control arm will take placebo or an established treatment regime. This allows comparison of the trial medication with placebo effects or conventional clinical practices. Therefore, data derived from an RCT study is generally regarded as the highest level of trial evidence by the scientific community. Moreover, data obtained from an RCT allows the research team and policy makers to assess if naltrexone maintenance therapy has definitive effectiveness, which is a major objective of the present study. Given the provision of promised resources, the research team thus expected the clinical research to achieve the highest level of scientific rigour, and be able to provide quality data of good reliability and validity.

The randomized controlled protocol was drawn up with a view to maximizing the scientific strength and value of the study.

3.1.3 Subsequent to the thorough discussion among members of the research team, a finalized protocol on RCT was submitted to the BDF by mid October 2002. The methodology of the RCT study was outlined as follows:

3.1.4 Study Design

3.1.4.1 The trial would be jointly conducted by the five SACs, located at the Kwai Chung Hospital, Pamela Youde Nethersole Eastern Hospital, Prince of Wales Hospital, Queen Mary Hospital, and Castle Peak Hospital.

3.1.4.2 Study Participants

3.1.4.2.1 A total of 180 recently detoxified opiate addicts would be recruited at the participating substance abuse clinics, methadone clinics[2] and NGO treatment centres.

3.1.4.2.2 One hundred and sixty participants would be randomized into treatment arm and placebo arm. These participants would receive

[2] Patients of methadone clinics who were maintained on low dose methadone (less than 15mg per day) could be referred to substance abuse clinics for inpatient detoxification.

4 months of supervised naltrexone maintenance therapy or placebo treatment. All participants would receive rehabilitative counselling. Upon completion of the naltrexone maintenance, all participants would be followed up for 6 months to monitor the outcomes. An independent cohort of 20 participants would be studied in an open trial manner. They would receive the same intervention and assessment as the participants in the intervention arm of the RCT, except that they would not receive supervision from the family/institution or the clinic.

3.1.4.2.3 Inclusion Criteria: Participants should fulfil the DSM-IV diagnostic criteria (a widely accepted research operational criteria) of opiate dependence. This meant that participants would have demonstrated clear evidence of withdrawal syndrome, physical dependence, and psychological dependence to heroin and/or methadone before they were detoxified. As previous studies showed that supervision and motivation were essential to the success of naltrexone maintenance, we would recruit only individuals who have family members or institutional workers (e.g. half-way house staff) to supervise the maintenance. For individuals who had no supervision from family or institutions, they would also be recruited if they could return to the SAC three times per week for supervised naltrexone intake. We would also recruit individuals who could return to the SAC three times per week for supervised naltrexone intake.

3.1.4.2.4 Exclusion Criteria: Participants would also be excluded if they 1) are below 18 or above 65 years old, 2) have uncontrolled heart disease, hypertension, diabetes mellitus, acute hepatitis or liver failure, 3) are women in pregnancy, 4) have mental illnesses and are unable to give accurate information, 5) have any other illnesses that require hospitalization, 6) are unable or unwilling to provide informed consent, or 7) plan to leave Hong Kong during the period of study.

Individuals who were addicted to other opiates, such as codeine in cough medicine, would not be recruited, as they deserved to be studied separately. Individuals who regularly administered other drugs with the heroin or methadone, as well as those who had alcohol or polysubstance abuse/dependence, would be excluded from the study.

3.1.4.2.5 Participants who fulfilled the abovementioned criteria would be invited to join the study. They would be explained the objectives, method, treatment, potential risks and benefits of the study in simple language. The study would begin only after the participant provided informed written consent.

3.1.4.3 Randomization

3.1.4.3.1 Participants of the RCT cohort would be randomized into treatment

and placebo arms by computer generated random number maintained by the project coordinator. The treatment group would receive 4 months of naltrexone maintenance plus rehabilitative counselling. The placebo group would receive 4 months of placebo and the same counselling as the treatment group. The placebo would bear the same appearance as the naltrexone tablets.

3.1.4.3.2 No additional psychotropic medications, including benzodiazepines, would be prescribed during the study period. Treatment for other medical condition, e.g. diabetes, would be continued.

3.1.4.3.3 Neither the subjects nor the rest of the investigating and management team would be aware of the treatment assignment. The coding would be kept by the project coordinator, who is reachable 24 hourly by pager. Each subject would receive a card that specified the nature of the drug trial as well as the contact pager number for decoding.

3.1.4.3.4 The drug would be unblinded if there were medical incidents, e.g. medical emergency, or if the patient left the drug trial. The size of partial unblinding would be assessed by asking the subjects, the investigating and management teams to guess the treatment assignments at the end of the study period.

3.1.4.4 Stratifications

3.1.4.4.1 Participants under the RCT design would be stratified into 2 layers: the first being participants who had family or institutional supervision, the second being participants who could return to clinic for supervised naltrexone treatment.

3.1.4.4.2 Stratified sampling was needed because it was known that the level of support and supervision was a strong determinant of outcome in naltrexone maintenance.

3.1.4.5 Procedure

3.1.4.5.1 Consented participants would be interviewed using the CATOM. Following the interview, the participants would receive a thorough physical examination, which would be followed by a liver function test. Naltrexone would be administered to the treatment group using the standardized regimes.

3.1.4.5.2 After a participant was detoxified and opioid free for 7 days, and his or her opioid-free condition verified by urine toxicology screen and naloxone challenge test[3] (0.8mg subcutaneously), treatment with naltrexone would begin with an initial dose of 25mg orally. Following the initial dose, the participant would be monitored for one hour. If no withdrawal sign occurred, the participant would be given another 25mg (i.e. the rest of the daily dose)[4]. Thereafter,

[3] Please refer to the Product Monogram for details.

[4] If signs or symptoms of withdrawal were present, administration of naltrexone would be delayed until the participant's drug using status was verified.

the participant would be given 50mg naltrexone per day orally[5].

3.1.4.5.3 The maintenance treatment would continue for 4 months and would be coupled with at least fortnightly rehabilitative counselling during maintenance phase. All rehabilitative counselling would be conducted by experienced drug abuse social workers or nurses.

3.1.4.6 Supervision

3.1.4.6.1 In the first stratum, participants would be supervised by their spouse or close family members for drug compliance. The family members would be taught by medical staff on how to improve and monitor drug compliance. Participants who resided in institution, e.g. half-way house, would be supervised by the staff, who would also receive training on how to improve and monitor drug compliance. The staff and the family members would be contacted by a clinic nurse or social worker on a regular basis for information support. Participants would be reviewed by substance abuse clinic psychiatrists on a fortnightly basis during the 4-month maintenance period. Naltrexone would be prescribed after each fortnightly review.

3.1.4.6.2 In the second stratum, participants would return to the clinic three

[5] Participants who did not have family supervision would return to the clinics three times a week. Their treatment regime was specified in the Procedure section.

times a week. They would take their naltrexone at the clinic under nursing supervision according to a thrice-weekly regime (100, 100, and 150mg naltrexone given on Monday, Wednesday, and Friday respectively). In other words, no naltrexone would be dispensed to the patients.

3.1.4.6.3 In order to ascertain the successful rate of naltrexone treatment in unsupervised context, an independent cohort of 20 participants would receive 4 months of naltrexone maintenance without family/institutional or clinical supervision. The study protocol would be exactly the same as the treatment arm of study one except that the participants would not have family/institutional or clinic supervision.

3.1.4.6.4 All participants would be monitored for drug compliance using the following means 1). self-reports, 2). pills counting, 3). urine tests to check for the presence (or absence) of naltrexone, and 4). reports from cohabiting family members if available. Subjects who had 1) significant non-compliance, 2) developed hypersensitivity, 3) intolerable side effects would be withdrawn from the study.

3.1.4.7 Treatment outcomes

3.1.4.7.1 The primary treatment outcomes were treatment retention/completion, opioid use under treatment, days to relapse

after detoxification, drug free days, and abstinence rate (as reported and verified with urine toxicology screening).

3.1.4.7.2 The secondary treatment outcomes were employment, criminal activities, family relationship, enrolment in rehabilitation treatment, treatment complying days (self-report), client satisfaction, side effects and mortalities. The outcomes would be assessed using the CATOM.

3.1.4.8 Handling of severe side effects/harms and accidental events

3.1.4.8.1 During the whole course of treatment, all participants would be under supervision of experienced addiction psychiatrists. Liver function would be monitored at baseline and each subsequent treatment month as recommended by the manufacturing pharmaceutical company.

3.1.4.8.2 When severe side effects or accident events occurred, the concerned participants would be withdrawn from the trial and the treatment allocation disclosed. The project coordinator could be contacted at all hours via a hotline for decoding.

3.2 Pilot Study of the RCT Study

3.2.1 The RCT pilot study was launched in early September 2003. During the course of recruitment, it was found that most eligible participants did not agree with the possibility of taking placebo. Hence, of 16 eligible

cases approached, only 6 (38%) agreed to participate in the study.

3.2.2 A total of six cases, five at the Kwai Chung Hospital and one at the Queen Mary Hospital, were successfully recruited for the pilot study. All cases were male, whose age ranged from 25 to 46 years old (mean age 36.5 years, $\pm$ SD 8.2 years). Of the participants 50% were married, and all of them were unemployed at the point of recruitment, and had been involved in criminal activity at least once in their lifetime.

3.2.3 Since one subject withdrew the study once finishing detoxification treatment, only 5 participants entered the naltrexone/placebo treatment trial. Randomly assigned to either treatment or control arm, 2 subjects were treated on naltrexone and the remaining on placebo. All of them were under the supervision of SAC nurse for naltrexone ingestion.

3.2.4 There were 5 cases dropped out of the study (83%). Of the 5 dropout cases, 1 withdrew once the inpatient detoxification was completed. One control subject withdrew from the study owing to self-report physical discomfort, and 2 defaulted the scheduled dispensing appointment and medical follow-up. Two participants, who were from the treatment and control arm respectively, completed the maintenance phase. However, the control case refused to proceed to the follow-up phase as he preferred to receive naltrexone treatment soon after the maintenance phase. Eventually, only one treatment

case proceeded to and eventually completed the 6-month follow-up phase.

> ■ **The pilot study of randomized controlled design showed that it was not feasible, and even dangerous, to conduct a naltrexone clinical controlled trial in the local drug abuse environment.**

3.2.5 Outcomes of the Pilot Study

3.2.5.1 Five of 6 participants dropped out from the study. The dropout rate is 83.3%.

3.2.5.2 The 2 cases who completed the maintenance treatment complied well with the 4-month naltrexone/placebo dispensing schedule. However, only one completed the 6-month follow-up.

3.2.5.3 With regard to the primary outcome, there was no relapse among the two participants who completed the maintenance treatment.

3.2.5.4 Secondary outcomes were as follows:

3.2.5.4.1 Employment: All participants were unemployed at the beginning of the study. While all the dropout cases remained unemployed at the time of termination, the case on maintenance treatment started doing a part-time job at the third month of the treatment.

3.2.5.4.2 Criminal Activities: One treatment case was detained by the police at week 4 and defaulted follow-ups thereafter.

3.2.5.4.3 Treatment Complying Days: One participant withdrew from the study before the treatment started. Two participants, each from the treatment and placebo arm, complied with the whole course of maintenance treatment (112 days). The mean number of treatment complying days (±SD[6]) for the treatment and control arm is 68.5 (±SD 61.5 days) and 46.3 (±SD 56.9 days) respectively. In other words, the retention rate of the treatment and control arm is 61% and 41% respectively. Since the sample size was too small for comparative analysis, no statistical test was performed.

3.2.5.4.4 There was no mortality or inpatient hospitalization.

3.2.5.4.5 No serious side effects were reported. Mild physical discomforts, including diarrhoea, dry mouth, reduced appetite, tremor and muscle stiffness, were reported by participants.

3.2.6 Insights of the RCT Pilot Study

3.2.6.1 The pilot study provided valuable information on the feasibility of the study design. The research team encountered a variety of problems in recruiting participants for the RCT. First, we found that

[6] SD = Standard Deviation

out of the 16 potential addicts we approached, 10 explicitly stated that they would not consider a trial that entailed the possibility of placebo. Of the 6 addicts enrolled, one dropped out after he opened the capsules and found placebo within. The pilot findings were discussed with supervisors and workers of local NGO drug abuse treatment agencies. Compatible with experience reported in the literature, the professional workers confirmed that our results were consistent with their experience, and opined that addicts' low self-esteem rendered study with obvious trial nature unacceptable. Essentially, many drug abusers resented the idea of being tested. They agreed to participate just to bet on the chances of being allocated to the naltrexone group. Past research on naltrexone treatment even reported that participants could distinguish easily whether the medication was "real" with one heroin injection (Kirchmayer et al, 2004). These clinical experiences underscored the complexities in blinding and randomisation.

3.2.6.2 In line with the experience of past clinical trials, high dropout rate (83%) is also reported in the present pilot study. The high attrition rate has been recognized as a hardly avoidable problem in the recruitment of drug addicts for clinical trial. Strain (2003) had justly pointed out that an important factor in the use of naltrexone is a matter of patient's level of motivation. However, their motivation to complete the whole study depended on many factors,

including psychological instability, which were unpredictable or hard to be controlled by the investigator. The consequence of the attrition problem was illustrated by Shufman et al.'s (1994) study, where the study design had to be changed because of the selective dropout in the first two weeks of treatment.

3.2.6.3 In addition, as long as trial culture is lacking in the local drug addiction community, it would be hard to recruit and retain participants in a trial within the placebo arm. As stated in the Cochrane Review (Kirchmayer et al, 2004), in many studies where blinding was done, dropout in the placebo group was much higher than that in the naltrexone group (e.g., Taintor et al, 1975). It further worsened the already unfavourable attrition rate, which rendered the continuation of any clinical trials impossible.

3.2.6.4 The unsatisfactory recruitment and attrition rate led the research team to reconsider the study design.

3.3 The Open Trial Design

When the randomized controlled study was found infeasible, the research team reconsidered an uncontrolled open trial for the study.

3.3.1 In view of the problems encountered in the pilot test of the RCT, the

research team proposed an open trial to overcome the problems.

3.3.2 The open trial study changed the focus from examining the efficacy of naltrexone treatment into the effectiveness of naltrexone maintenance therapy in the local context, i.e. the RCT design focused on pharmacology, while the open trial design focused on how the drug acted in real life situation.

3.3.3 In the open trial, a total of 160 detoxified opiate addicts would be recruited. All participants would receive 4 months of supervised naltrexone maintenance therapy plus rehabilitative counselling. Upon completion of the naltrexone maintenance, they would be followed up for 6 months to monitor the outcomes.

3.3.4 Concerns of the Ethics Committee of the CUHK

The Clinical Ethics Committee of the CUHK concerned whether an uncontrolled open trial would be able to provide data with sufficient scientific quality to inform policy makers for decisions.

3.3.4.1 After the open trial design protocol was drawn up, the research team applied for ethics approval with the EC of the Chinese University of Hong Kong for conversion of the study design.

3.3.4.2 The EC raised some concerns relating to the study design in February 2004. First, the EC opined that the sample size of 160 patients to receive naltrexone maintenance therapy was too large. Justification was required. Furthermore, the EC suggested that the revised protocol should explain how the control group would be formed and compared with the naltrexone group.

3.3.4.3 The rationale for the above was that since open trial was generally of exploratory nature, the usual sample size should be much smaller than 160. This aimed at minimizing the number of participants exposed to risky intervention. The EC was also concerned about the absence of control comparison, which rendered meaningful interpretation of study results difficult, i.e. whether naltrexone was any better than that of a conventional treatment approach or placebo remained questionable.

3.4 Considerations of Alternative Study Designs

A number of alternative designs have been considered and discussed. It was agreed that it was impossible to recruit suitable control group for comparison under the current drug treatment service context.

3.4.1 The research team consulted experts on psychopharmacology, research methodology and trial design. These experts confirmed that

the concerns raised by the EC were legitimate. The research team also discussed with these experts and the MG regarding the appropriate response to the comments. The discussion was summarized as follows.

3.4.2 To fulfil the study objectives, a large-scale controlled clinical trial, involving SACs, Methadone Clinics and all local NGO drug abuse treatment agencies, was required.

3.4.3 However, as mentioned above, RCT had been proved to be non-feasible in the local context. Other control designs, therefore, had been considered:

3.4.3.1 *To compare the results of the current study with benchmark data of other relapse prevention services.* To facilitate a meaningful comparison of treatment outcomes, data regarding the effectiveness of other relapse prevention services would be needed. This would essentially become an evaluation study of the service performance of participating agencies, which might provoke agencies' resistance to provide data for analysis.

3.4.3.2 *To compare the results of the current study with past treatment data of the participants.* It would also be hard to use past treatment data (e.g. the abstinence period of previous treatment) of individual participants as self-control comparison. This was because the retrospective data were generally not properly documented and subject to recall bias.

3.4.3.3 *To divide participants into two groups, provide one group with naltrexone treatment and another group without any treatment, and then compare the outcomes.* It was also not feasible in the local context since we anticipated problems in recruitment and high dropout rate as participants generally preferred a quick fix to their problems.

3.4.4 It revealed that none of the alternative designs were able to recruit suitable control group for scientifically sound comparison under the current drug treatment service context to fully address the objectives of the study in a scientifically rigorous manner.

3.5 Finale of the study

3.5.1 As a result of the above considerations, the research team concluded that a large-scale controlled clinical study was unable to be conducted in Hong Kong. We, therefore, have considered carrying out a small-scale open trial study with control comparison in response to the EC's first concern. However, such a small-scale study is unable to demonstrate sufficient power for statistical analysis, and thus lacks precision to provide reliable answers to fulfil the study objectives.

3.5.2 The risks of a naltrexone treatment study in Hong Kong had also been taken into consideration. First, the participants were predominantly

outpatient. Instead of being confined in a drug-free residential setting, such as hospitals and correctional institutes, an outpatient service was difficult, if not impossible, to prevent the study participants staying away from high-risk environment. Detoxified participants, unavoidably, would be subject to the risk of relapse, which might be a fatal one.

3.5.3 In addition, a controlled trial involving placebo would potentially be more dangerous. There was misunderstanding that naltrexone has "Antabuse"-like effect for heroin, and many of the eligible participants considered testing the effectiveness of the naltrexone blockade by a shot of heroin. Such testing practice was dangerous and might lead to accidental overdose and even mortality.

3.5.4 In brief, the research team found that RCT study was not feasible. Second, it was impossible to identify control comparison for an open trial. In the absence of control arm, an open study would not be able to generate data of adequate scientific quality. Such data were unlikely to be useful for policy decision. Last, whatever design to take, the risk of overdose for naltrexone maintenance trial would be substantial.

3.5.5 Since it appeared that it was not possible to conduct a large-scale study to test effectiveness of naltrexone maintenance in Hong Kong, the MG concluded that the study should be winded up at that juncture.

The research team decided to wind up the study because further research activity would be unlikely to contribute data with sufficient scientific strength to inform policy makers. Following thorough discussions and consultations, it was concluded that there was no appropriate study design to evaluate the effectiveness of naltrexone in Hong Kong.

3.5.6 It should be noted that premature termination of a clinical trial was not uncommon if the study design was found inappropriate in practical setting. In the same vein, as safeguarding people's safety always takes precedence in all clinical studies, it was logical and conscientious to wind up a trial if potential risks endangered participants' safety. Therefore, given the recruitment problems and underlying risks pertaining to the naltrexone study, it was a responsible action to terminate the study prematurely at this stage.

Chapter 4. Conclusions

4.1 Based on the scientific evidence available to date, as well as our own experience accumulated from the present study, subsidized naltrexone maintenance therapy is not recommended to be provided in Hong Kong.

4.2 Furthermore, it is important to note that according to the Cochrane Review, there were a total of 11 trials on naltrexone maintenance, and there were both positive and negative studies. The latest Cochrane Review of naltrexone maintenance thus concluded that there was insufficient scientific evidence to allow judgment of the efficacy of naltrexone maintenance.

4.3 Experience accumulated

4.3.1 The study pioneered a multi-centre drug trial study in the field of substance abuse treatment in Hong Kong. Confined by a number of inherent limitations, the research team has come across considerable practical difficulties that hindered the completion of the study. These difficulties, together with the valuable experience accumulated in the study, have given us precious insights into the research culture of the local drug abuse environment. The experience shared here will be useful for future clinicians and researchers.

4.3.2 Subjects' Preference for Trial Design:

4.3.2.1 During the recruitment stage of the study, the research team was intrigued by the subjects' preference for different trial designs. We found that only a handful of detoxified abusers showed interest in participating in a randomized controlled trial (RCT) study while the majority expressed resistance to bear the possibility of taking placebo. On the one hand, when subjects from the Society for the Aid and Rehabilitation of Drug Abuse (SARDA) were recruited to the open trial, the majority of SARDA halfway house residents showed great enthusiasm in participation. Such preference difference might imply that a satisfactory enrolment rate would be achieved if the clinical trial of naltrexone maintenance treatment were provided on a service modality of open trial design.

4.3.3 Compliance Level of Participants:

4.3.3.1 Although the experience of SARDA may infer a potential solution to the recruitment problem, whether these participants are able to commit a maintenance treatment lasting as long as a quarter of year remains uncertain. As suggested by Carroll (2002), the absence of a reinforcing drive for ingestion, as well as negative consequences with abrupt discontinuation, would lead to high rates of attrition and poor compliance with naltrexone treatment. Hence, in Australia, where naltrexone maintenance treatment is widely applied, only a relatively small proportion of heroin users were able

to stay in naltrexone treatment for a duration of 3 months or longer (Bell et al., 2003).

4.3.3.2 In our RCT pilot study, 2 of 6 cases successfully completed the 4-month maintenance treatment. The retention rate (33%) is better than that of the Castle Peak Hospital trials (17%). However, because of the small sample size, the outcome observed here lacks statistical power to draw a meaningful inference to the local situation.

4.3.4 Subgroup of Clientele Most Profited from Naltrexone Therapy:

4.3.4.1 Although naltrexone therapy has not yet been considered as a maintenance treatment with scientifically-proven superiority to other forms of treatment, naltrexone may be an efficacious addition to the existing therapy, especially for certain target groups including detoxified drug addicts with good motivation or faced with certain contingencies. Furthermore, some circumstances may increase the probability of a positive outcome of naltrexone treatment, such as stable social contacts, occupation, confidential relationship with the therapist, and so forth (Kirchmayer et al, 2004).

4.3.4.2 Operated on an outpatient modality, our maintenance treatment should target at the subgroup of clienteles who are able to demonstrate motivation in rehabilitation and are equipped with

stable supporting network. Detoxified users receiving aftercare services (e.g. counselling, halfway houses etc.), as well as those with family support are the desirable candidates who will most likely benefit from the naltrexone treatment should it be implemented in Hong Kong. In line with our experience of the RCT pilot study, this subgroup of clientele will be suitable to receive naltrexone treatment based on the condition that their ingestion of medication would be closely supervised, and the rehabilitation process be constantly monitored.

4.3.5 Enhancement of Self-Monitoring Ability:

4.3.5.1 While low compliance rate seems to be the crux of a naltrexone maintenance trial, better outcomes were achieved by patients who were able to complete the treatment. Some previous studies have reported a positive correlation between the length of treatment and improved rehabilitation of the patient (Greenstein et al, 1981; Ling and Ronald, 1984). And as stated in the Clinical Guidelines and Procedure for the Use of Naltrexone (Bell et al, 2003), a significant proportion of people, who had stayed in naltrexone treatment for 3 months or longer, would be able to remain abstinent from heroin.

4.3.5.2 In fact, owing to the high affinitive property of naltrexone to opioid receptors, it has been reported in literature that a single lapse would not trigger the reinforcement cycle as easily as other treatment methods. Apart from the pharmacological effect, the

efficacy of naltrexone lies on its effect on psychosocial aspect as well. In particular, as a result of the blockade effect of naltrexone, administering naltrexone would not produce any internal or external reinforcement mechanism in the course of treatment. The medication works as a constant reminder to the client to stay away from heroin. Therefore, detoxified users who could comply with the treatment and maintain abstinence would benefit from the medication by strengthening self-efficacy.

4.3.6 Improvement of Family Relationship:

4.3.6.1 Significant improvement of family relationship was found in participant most benefited from the naltrexone treatment. It is to our clinical experience that the unsupportive attitude of the family would easily frustrate a vulnerable detoxified addict, and a quick lapse is not uncommon. Harbouring doubts and distrust, some family members would hold a suspicious attitude towards the verbal commitment of their family member with drug problems. Without mutual trust and confidence, excessive questionings from family members, be it a monitor or concern, would only cause irritation and frustration in detoxified users. Even worse, emotional instability thus resulted would easily prompt the detoxified users to resort to drugs again.

4.3.6.2 On the other hand, compliance with naltrexone maintenance treatment, which works like a shield from illicit drugs, could

promote trust and confidence. Family would be more willing to give credit to the participants who were able to show their self-motivated determination by actions. Furthermore, improved communication would mend the fractured family bond, which in turn lead to a more favourable outcome in the treatment. The case story of Mr. X (below), who is one of our pilot study cases, would illustrate how the naltrexone maintenance therapy has positively changed his life.

CASE STUDY

Mr. X, a mid-forties heroin addict for years, took part in the pilot study of naltrexone maintenance therapy. He had made several attempts on his own, but could only maintain abstinence for not more than a couple of months at best. This was his first attempt of pharmacology treatment for his drug abuse problem.

Mr. X came to us as a frustrated man living an unhappy life. What made him feel really bad was the worsening family relationship. He was particularly annoyed by the repeated questionings from his discontented wife, which commonly ended in rows and quarrels. Distrust, anger, disappointment, and frustration fueled the family dynamics with negative affects.

So what had been working on to motivate Mr. X to take the treatment? He attributed his motivation to his dear newborn in hope of rebuilding a good father figure. Intrinsically motivated, Mr. X complied closely with the treatment schedule. He regarded the outcome of the treatment as favourable, like improved sleeping quality, few physical discomforts, and disappearance of sudden craving. In general, he felt good about himself.

With hope and confidence, Mr. X resumed the role of a breadwinner in the family. Being employed as a part-time waiter, Mr. X was happy about his new job, and even more enjoyed the improved family life. His wife, witnessing the dramatic change occurred, regained confidence in her husband. Reduced questionings had also helped rebuilding a trusting relationship. Though he admitted that he would still worry about the future sometimes, he indeed felt much satisfied about his present life. Mr. X successfully completed the maintenance therapy and remained abstinent 6 months afterward.

4.3.7 Common Myths about Naltrexone:

4.3.7.1 As a result of inadequate knowledge and partial information, myths and misunderstandings about the effects of naltrexone prevailed within the drug abuse community. Some drug users have expressed their worries about being hooked on to naltrexone after the lengthy treatment, despite the fact that naltrexone has no opioid agonist effects. Other detoxified opioid users have described naltrexone as being a form of "antidote" to heroin addiction, which could be used to "cure" a sudden temptation to use heroin. However, previous clinical experience informed that patients who took naltrexone in the hope that it would wipe out their desire to use heroin, or would maintain their motivation to remain abstinent, were disappointed.

4.3.7.2 Even worse, not only the drug abusers, but also the social workers, who lack training and knowledge of naltrexone use, uphold similar kinds of misunderstanding. Therefore, education and accurate information are essential to all parties involved in the handling of naltrexone. These include but are not limited to social workers, institutional staff, supportive family members, and most importantly, the drug users themselves.

10 Common Myths about Naltrexone

- ✗ "Naltrexone, like methadone, is essentially another hook that resembles heroin."
- ✗ "Naltrexone must be taken for life. Once I drop out, I will lose the protection against craving."
- ✗ "I know that naltrexone cannot be taken with heroin at the SAME time. So I can resume naltrexone shortly after taking heroin."
- ✗ "It won't do harm to take a lapse while using naltrexone, if only I tried out bit by bit and don't take too much heroin at one time."
- ✗ "Naltrexone is an 'Antabuse'-like medication. It 'cures' heroin addiction."
- ✗ "Naltrexone is an aversive therapy. Naturally I will be sick of heroin after the treatment. So I will be absolutely safe in high risk situations."
- ✗ "Naltrexone can help eliminate all the residual toxicant out of the body."
- ✗ "Naltrexone will always keep me highly motivated to remain abstinent."
- ✗ "Naltrexone is a dominating (霸道) drug. It will fight against heroin and make me feel turbulent inside my body."
- ✗ "Naltrexone works like Panadol. Whenever the sudden craving attacks, take one to wipe out the craving. Desire will subside immediately."

4.3.8 Management of Naltrexone Use:

4.3.8.1 Given that there are a lot of myths about the effects of naltrexone in the drug community, the administration and dispensing of naltrexone are irrefutable duties of medical professionals. During the process of recruitment, we were astonished that even if the users fathomed well about the blockade effect of naltrexone, many still openly disclosed themselves as a ready-to-go experimenter. In an attempt to surmount the pharmacological effects, the drug users would test out the ceiling levels by progressive dose of heroin, which was an extremely dangerous behaviour that posed their own life at stake. These incidents have been widely reported both locally and overseas.

4.3.8.2 With the presence of these potential risks, the administration of naltrexone, including prescription, dispensing, regular check-up etc., must be carefully monitored by professionally led team.

Highlights of Experience Earned from the Study

- Patients showed inclination to open trial study. Recruitment problems might be solved if the trial is conducted on service basis.
- Compliance level of local patients to naltrexone treatment remains uncertain.
- Patients who are compliant to the treatment benefit through enhanced self-efficacy and improved family relationship.
- Naltrexone may be effective in a subgroup of heroin addicts who are motivated and have strong family support.
- There are a lot of myths about the effects of naltrexone in the field of drug abuse, which may increase the risk of heroin toxicity.
- Decision of prescribing naltrexone should be tailored made by doctors who had expertise in heroin addiction and naltrexone.

Appendices I to IV

Appendix I: List of Overseas Studies of Naltrexone Maintenance

Author(s)	Year	Title	Source
Ali R, McGregor JMW, Thomas P, Gowing L	2001	A randomized controlled trial of antagonist-precipitated heroin withdrawal under anesthetic prior to naltrexone maintenance: outcomes at 6 and 12 months	Drug and Alcohol Dependence, 63 Suppl 1, p.6
Alison J. Ritter	2002	Naltrexone in the treatment of heroin dependence: relationship with depression and risk of overdose	Australia and New Zealand Journal of Psychiatry 2002; 36:224-8
Arnold-Reed DE, Hulse GK, Hansson RC, et al	2003	Blood Morphine levels in naltrexone-exposed compared to non-naltrexone-exposed fatal heroin overdoses.	Addiction Biology 8(3): 343-350
Azaian A, Papiasvili A, Joseph H	1994	A study of the use f clonidine and naltrexone in the treatment of opioid addiction in the former USSR.	Journal of Addictive Diseases, 13(1), p.35-52
Bearn J, Bennett J, Martin T, Gossop M, Strang J	2001	The impact of naloxone/lofexidine combination treatment on the opiate withdrawal syndrome.	Addiction Biology, 6(2), p.147-156
Bell J., Kimber J., Lintzeris N., White J., Monheit B	2003	Clinical Guidelines and Procedures for the Use of Naltrexone in the Management of Opioid Dependence	Publications Production Unit, Australian Government Department of Health and Aging
Bradford A, Hurley F, Golondzowski O, Dorrier C	1976	Interim report on clinic intake and safety data collected from 17 NIDA-funded naltrexone studies	NIDA Research Monograph, 9, p.163-71
Brahen LS, Capone T, Heller RC, Linden SL, et al	1978	Controlled clinical study of naltrexone side effects comparing first-day doses and maintenance regimens	American Journal of Drug and Alcohol Abuse, 5(2), p.235-45
Brahen LS, Capone T, Wiechert V, Desiderio D	1977	Naltrexone and cyclazocine. A controlled treatment study *	Archives of General Psychiatry, 34(10), p.1181-4
Brahen LS, Capone T, Wojak JC	1979	The double-blind crossover trial design: how good is it for psychoactive drugs?	American Journal of Drug and Alcohol Abuse, 6(2), p.189-96
Callahan E, Rawson R, Glazer M, et al	1976	Comparison of two naltrexone treatment programs: naltrexone alone versus naltrexone plus behavior therapy.	NIDA Research Monograph, 9, p.150-7
Callahan EJ, Rawson RA, McCleave B, et al	1980	The treatment of heroin addiction: Naltrexone alone and with behavior therapy.	International Journal of the Addictions, 15(6), p.795-807
Carroll KM, Ball SA, Nich C, et al.	2001	Targeting behavioral therapies to enhance naltrexone treatment of opioid dependence: efficacy of contingency management and significant other involvement	Archives of General Psychiatry, 58(8), p. 755-61
Carroll KM, Sinha R, Nich C, et al.	2002	Contingency management to enhance naltrexone treatment of opioid dependence: a randomized clinical trial of reinforcement magnitude	Experimental & Clinical Psychopharmacology, 10(1), p.54-63
Charney DS, Redmond DE Jr, Galloway MP, et al	1984	Naltrexone precipitated opiate withdrawal in methadone addicted human subjects: evidence for noradrenergic hyperactivity.	Life Sciences, 35(12), p.1263-72

Author(s)	Year	Title	Source
Collins ED, Whittington RA, Heitler NE, Klebe HD	2001	A randomized comparison of anesthesia-assisted heroin detoxification with buprenorphine and clonidine assisted detoxifications.	Drug and Alcohol Dependence, 63 Suppl 1, p.30
Comer SD, Collins ED, et al.	2002	Depot naltrexone: Long-lasting antagonism of the effects of heroin in humans.	Psychopharmacology 159(4): 351-360
Cornish JW, Metzger D, Woody GE, et al	1997	Naltrexone pharmacotherapy for opioid dependent federal probationers. *	Journal of Substance Abuse Treatment, 14(6), p.529-34
Curran S, Savage C	1976	Patient response to naltrexone: issues of acceptance, treatment effects, and frequency of administration. *	NIDA Research Monograph Series, 9, p.67-9
Dean AJ, Jones RT, and Saunders JB	2002	Psychological symptoms during naltrexone treatment: findings from a randomized controlled trial	International Journal of Neuropsychopharmacology, 5, Suppl 1, p.158
Digusto E., Shakeshaft, A., Ritter A., O'Brien S.; Mattrick RP., and the NEPOD Research Group	2004	Serious advers events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD)	Addiction, 99: 450-60
Farren CK, O'Malley S	2002	A pilot double blind placebo controlled trial of sertraline with naltrexone in the treatment of opiate dependence.	American Journal on Addictions, 11(3), p.228-34
Ferri M. , Davoli M. , Perucci C.A.	2004	Heroin maintenance for chronic heroin dependence.	The Cochrane Library, Issue 1, 2004.
Fulghesu AM, Lanzone A, Apa R, Guido M, et al	1997	The hypothalamic-pituitary-luteal axis in women: effects of long-term orally active opioid antagonist (naltrexone) administration.	Journal of Endocrinological Investigation, 20(7), p.368-73
Gerra G, Fertonani AG, Caccavari R, et al	1994	Gamma-hydroxy-butyric acid in the treatment of heroin addiction.	New Trends in Clinical Neuropharmacology, 8(2-4), p.357-62
Gerra G, Fertonani G, Zaimovic A, et al	1995	Hostility in heroin abusers subtypes: fluoxetine and naltrexone treatment.	Progress in Neuro-Psychopharmacology & Biological Psychiatry,19(8)p.1225-37
Grau, S., Salas, E., and Del Villar, T. A.	1989	Riboflavin marker of naltrexone and placebo capsules as an index of compliance	Farmacia Clínica, 6(10), p.758-60
Greenstein RA, O'Brien CP, McLellan AT, et al	1981	Naltrexone: A short-term treatment for opiate dependence.	American Journal of Drug Alcohol Abuse 8: 291-300
Grey C, Osborn E, Reznikoff M	1986	Psychosocial factors in outcome in two opiate addiction treatments *	Journal of Clinical Psychology, 42(1), p.185-9
Hall, Wayne D	1999	Is naltrexone a cure for heroin dependence? The evidence so far is not promising	The Medical Directory of Australia, 171: 9-10
Hulse, GK & Basso, MR	2000	The association between naltrexone compliance and daily supervision	Drug and Alcohol Review 19: 41-48

APPENDIX I

Author(s)	Year	Title	Source
Hollister LE, Bearman JE, Duster TS, et al	1978	Clinical evaluation of naltrexone treatment of opiate-dependent individuals *	Archives of General Psychiatry, 35(3), p.335-40
Hollister LE, Johnson K, Boukhabza D, Gillespie HK	1981	Aversive effects of naltrexone in subjects not dependent on opiates.	Drug and Alcohol Dependence, 8(1), p.37-41
Jelovac N , Milas M , Golik-Gruber V	2000	Naltrexone is efficient in maintaining heroin abstinence of selected groups of addicts.	Alcoholism, 36(1), p.73-7
Jepsen PW	1990	Naltrexone. An opioid antagonist to support the drug-free state in previous opioid addicts having stopped the habit	Ugeskrift for Laeger, 152(36), p.2546-9
Judson BA, Carney TM, Goldstein A	1981	Naltrexone treatment of heroin addiction: efficacy and safety in a double-blind dosage comparison.	Drug and Alcohol Dependence, 7(4), p.325-46
Judson BA, Goldstein A, Inturrisi CE	1983	Methadyl acetate (LAAM) in the treatment of heroin addicts. II. Double-blind comparison of gradual and abrupt detoxification.	Archives of General Psychiatry, 40(8), p.834-40
Kaiko RF, Grandy RP, Reder RF, et al	1995	A bioequivalence study of oral controlled-release morphine using naltrexone blockade.	Journal of Clinical Pharmacology, 35(5), p.499-504
Keegan J, Lavenduski C, Schooff K	1976	Comments and findings from a naltrexone double blind study	NIDA Research Monograph, 9, p.74-6
Kirchmayer U., Davoli M., Verster A.	2004	Naltrexone maintenance treatment for opioid dependence.	The Cochrane Library, Issue 1, 2004.
Kirchmayer U., Davoli M., Verster A. et al	2002	A systematic review on the efficacy of naltrexone maintenance treatment in opioid dependence.	Addiction, 97, p.1241-1249
Kleber HD, Kosten TR, Gaspari J, Topazian M	1985	Nontolerance to the opioid antagonism of naltrexone.	Biological Psychiatry, 20(1), p.66-72
Kosten TR, Krystal JH, Charney DS, et al	1990	Opioid antagonist challenges in buprenorphine maintained patients.	Drug & Alcohol Dependence, 25(1), p.73-8
Kosten TR, Morgan C, Kleber HD	1992	Phase II clinical trials of buprenorphine: detoxification and induction onto naltrexone.	NIDA Research Monograph, 121, p.101-19
Krupitsky E, Zvartau E, Masalov D, et al.	2002	Double-blind placebo-controlled randomized clinical trial of naltrexone for heroin addiction and HIV risk reduction in Russia	Drug and Alcohol Dependence, vol.66 suppl1
Krupitsky EM, Zvartau EE, Neznanov NG, et al	2001	A double blind placebo controlled clinical trial of naltrexone for heroin addiction in Russia: sample characteristics and short term follow-up	Drug and Alcohol Dependence, 63 Suppl 1, p.84
Ladewig D	1990	Naltrexone - an essential support in the psychosocial rehabilitation process of former dependence on opiates *	Therapeutische Umschau, 47(3), p.247-50

Author(s)	Year	Title	Source
Landabaso MA, Iraurgi I, Jimenez-Lerma JM, et al	1998	A randomized trial of adding fluoxetine to a naltrexone treatment programme for heroin addicts	Addiction, 93(5), p.739-44
Lerner A, Sigal M, Bacalu A, et al	1992	A naltrexone double blind placebo controlled study in Israel *	Israel Journal of Psychiatry & Related Sciences, 29(1), p.36-43
Ling W, Ronald RW	1984	Naltrexone treatment for addicted health-care professionals: A collaborative private practice experience.	Journal of Clinical Psychiatry 45: 46-48
Lozano Polo JL, Gutierrez Mora E, Martinez Perez V, et al	1997	Effect of methadone or naltrexone on the course of transaminases in parenteral drug users with hepatitis C virus infection	Revista Clinica Espanola, 197(7), p.479-83
Marrazzi MA, Wroblewski JM, Kinzie J, Luby ED	1997	High-dose naltrexone and liver function safety.	American Journal on Addictions, 6(1), p.21-9
Martin WR, Jasinski DR, Mansky PA	1973	Naltrexone, an antagonist for the treatment of heroin dependence. Effects in man.	Archives of General Psychiatry, 28(6), p.784-91
McDonald T, Berkowitz R, Hoffman WE	2000	Plasma naltrexone during opioid detoxification.	Journal of Addictive Diseases, 19(4), p.59-64
McGregor C, Ali R, White JM, et al.	2002	A comparison of antagonist-precipitated withdrawal under anesthesia to standard inpatient withdrawal as a precursor to maintenance naltrexone treatment in heroin users: outcomes at 6 and 12 months	Drug and Alcohol Dependence, vol.68 (1), p.5-14
Mello NK, Mendelson JH	1980	Buprenorphine suppresses heroin use by heroin addicts	Science, 207(4431), p.657-9
Mello NK, Mendelson JH, Kuehnle JC, Sellers MS	1981	Operant analysis of human heroin self-administration and the effects of naltrexone. *	Journal of Pharmacology & Experimental Therapeutics, 216(1), p.45-54
Meyer MC, Straughn AB, Lo MW, et al	1984	Bioequivalence, dose-proportionality, and pharmacokinetics of naltrexone after oral administration	Clinical Psychiatry, 45(9II), p.15-9
Miotto K., McCann M., Basch J., et al	2002	Naltrexone and Dysphoria: Fact or Myth?	The American Journal on Addictions, 11:151-160
Miotto K., McCann M., Rawson RA., et al	1997	Overdose, suicide attempts, and death among a cohort of naltrexone-treated opioid addicts.	Drug Alcohol Depndence, 45: 131-4
Morral AR, Iguchi MY, Kirby KC, et al	1998	Reinforcing therapeutic behaviors: preliminary results from a two-site detoxification study	CPDD, p.99
Morris Philip	2002	International studies with naltrexone	155th Annual Meeting of the APA; 2002 May 18-23rd; Philadelphia, PA, USA
Navaratnam V, Jamaludin A, Raman N, et al	1994	Determination of naltrexone dosage for narcotic agonist blockade in detoxified Asian addicts.	Drug & Alcohol Dependence, 34(3), p.231-6
National Drug and Alcohol	2001	National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD): Report of	NDARC

Author(s)	Year	Title	Source
Research Centre		Results and Reommendtions	
O'Malley Stephanie S, O'Connor Patrick G, et al	2002	Naltrexone: effect of therapy and treatment duration	155th Annual Meeting of the APA; 2002 May 18-23rd; Philadelphia, PA, USA
O'Malley, SS, Farren, CK, Namkoong, K, et al	2000	Naltrexone: effect of therapy and treatment duration	153rd Annual Meeting of the APA; 2000 May 13-18th; Chicago, Illinois, USA
Osborn C, Benziger D, Henderson J, Ehrich E, et al	2000	Sustained, 30 day therapeutic levels of naltrexone in a phase I clinical study	39th Ann. Meet. of American College of Neuropsychopharmacology. Dec10-14, 2000; San Juan; Puerto Rico
Osborn E, Grey C, Reznikoff M, et al	1986	Psychosocial Adjustment, Modality Choice, and Outcome in Naltrexone versus Methadone Treatment	American Journal of Drug and Alcohol Abuse, 12(4), p.383-8
PektaSNO, Kalyonko ÖA, Mirsal H, et al	1998	Different forms (oral or implant) of naltrexone use in relapse prevention on heroin addicts: a controlled clinical trial up to 6 months follow-up.	XXIst Collegium International Neuro-psychopharmacologicum, Glasgow, Scotland.12-16 Jul, 98
Pfohl DN, Allen JI, Atkinson RL, et al	1986	Naltrexone hydrochloride (Trexan): a review of serum transaminase elevations at high dosage.	NIDA Research Monograph, 67, p.66-72
Preston KL, Silverman K, Umbricht A, et al	1999	Improvement in naltrexone treatment compliance with contingency management.	Drug & Alcohol Dependence, 54(2), p.127-35
Rawson RA, Glazer M, Callahan EJ, Liberman RP	1979	Naltrexone and Behaviour Therapy for Heroin Addiction *	NIDA Research Monograph, 25, p.26-43
Resnick RB, Washton AM, Stone Washton N	1981	Psychotherapy and naltrexone in opioid dependence. Problems of Drug Dependence, 1980.	NIDA Research Monograph Series, 34, p.109-15
Rothenberg JL, Sullivan MA, Bornstein G, et al.	2002	Behavioral naltrexone therapy: Efficacy of a new behavioral treatment for heroin dependence and future directions	Drug and Alcohol Dependence, vol.66 suppl1
Rounsaville BJ, Carroll KM, and Fenton LR	1998	Enhancing naltrexone treatment after detoxification	151st Ann. Meeting of the APA. Toronto, Ontario, Canada. 30th May-4th June 1998
Salem HT, Salah M, Kotb HI et al	1997	The use of specific opioid receptor antagonist (naltrexone) in hypertensive pregnancy	Research Activities on Reproductive Health
San L, Pomarol G, Peri JM, Olle JM, Cami J	1991	Follow-up after a six-month maintenance period on naltrexone versus placebo in heroin addicts. *	British Journal of Addiction, 86(8), p.983-90
San L, Puig M, Bulbena A, Farre M	1995	High risk of ultrashort noninvasive opiate detoxification	American Journal of Psychiatry, 152(6), p.956
Saunders JB, Jones R, Dean A, et al	2002	Comparison of rapid opiate detoxification and naltrexone with methadone maintenance in the treatment of opiate dependence: A randomized controlled trial	Drug and Alcohol Dependence, vol.66 suppl1
Schuh KJ, Walsh SL, Stitzer ML	1999	Onset, magnitude and duration of opioid blockade produced by buprenorphine and	Psychopharmacology, 145(2), p.162-74

Author(s)	Year	Title	Source
		naltrexone in humans	
Shufman EN, Porat S, et al	1994	The efficacy of naltrexone in preventing reabuse of heroin after detoxification. *	Biological Psychiatry, 35(12), p.935-45
Silverstone PH, Attenburrow MJ, Robson P	1992	The calcium channel antagonist nifedipine causes confusion when used to treat opiate withdrawal in morphine-dependent patients.	International Clinical Psychopharmacology, 7(2), p.87-90
Sivolap IuP, Savchenkov VA	1998	Preventive therapy of opiate addiction with naltrexone	Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova, 98(11), p.22-5
Sobel BFX, Liesbon IA, Bigelow GE	2001	Prolonged opioid blockade by depot naltrexone (Naltrel TM)	Drug and Alcohol Dependence, 63 Suppl 1, p.148
Stella L, Cassese F, Barone S, et al	1999	Naltrexone to keep a drug-free condition	Research Communications in Alcohol & Substances of Abuse, 20(3-4), p.91-98
Stimmel B	2001	Maintenance therapy for opioid addiction with methadone, LAAM and buprenorphine: the Emperor's New Clothes Phenomenon.	Journal of Addictive Diseases, 20(4), p.1-5
Stran, Eric C	2003	Commentary of Review: there is insufficient evidence for naltrexone maintenance treatment in opioid dependence	Therapeutics EBMH May 2003, vol.6, 57
Taintor Z., landsberg, R. & Wicks, N.	1975	Experiences with naltrexone in Buffalo.	American Journal of Drug and Alcohol Abuse, 2, 391-401
Thomas M, Kauders F, Harris M, Cooperstein J, et al	1976	Clinical experiences with naltrexone in 370 detoxified addicts.	NIDA Research Monograph, 9, p.88-92
van Dyck CH, Rosen MI, Thomas HM, et al	1994	SPECT regional cerebral blood flow alterations in naltrexone-precipitated withdrawal from buprenorphine.	Psychiatry Research, 55(4), p.181-91
Volavka J, James B, Reker D, et al	1979	EEG and other effects of naltrexone and heroin in man.	Pharmakopsychiatrie Neuro-Psychopharmakologie, 12(1), p.79-85
Volavka J, Resnick RB, Kestenbaum RS, Freedman AM	1976	Short term effects of naltrexone in 155 heroin ex addicts	Biological Psychiatry, 11(6), p.679-85
Volpicelli Joseph R, Monterosso John Pettinati Helen M	2002	Naltrexone: effects of treatment duration	155th Annual Meeting of the APA; 2002 May 18-23rd; Philadelphia, PA,
Volpicelli, JR, Monterosso, J, and Pettinati, HM	2000	Naltrexone: effects of treatment duration	153rd Annual Meeting of the APA; 2000 May 13-18th; Chicago, Illinois
Yuen KH, Peh KK, Billa N	1999	Comparative bioavailability study of a generic naltrexone tablet preparation	Drug Development & Industrial Pharmacy, 25(3), p.353-6

Note: * Studies included in the Cochrane Library

Appendix II: List of Chinese Studies of Naltrexone Maintenance

Author(s)	Year	Title	Source
郭玉輝,蔣中亮,李玉屏	2003	推行整体護理模式提高納曲酮的服用率	中國藥物濫用防治雜志, 2003, 9(1)
劉運琴,戢漢兵	2003	納曲酮用于海洛因依賴治療	中國藥物依賴性雜志, 2003, 12(3), 198-200
張志祥,葉浩,張步振,程琳霞,徐貴麗	2002	鹽酸納曲酮預防海洛因依賴戒斷后复吸的臨床觀察	西南國防醫藥, 2002, 12(3), 246-7
靳方,吉順利,耿云濤	2002	納曲酮兩种給藥方法依從性的比較	中國藥物依賴性雜志, 2002, 11(2), 129-130
Guo S, Jiang Z, Wu Y	2001	Efficacy of naltrexone hydrochloride for preventing relapse among opiate-dependent patients after detoxification.	Hong Kong Journal of Psychiatry, 11(4), p.2-8
王文甫	2001	海洛因依賴者服納曲酮抗复吸治療期間濫用海洛因的原因及對策	中國藥物濫用防治雜志, 2001, 32(3), 32-4
李禎英	2001	納曲酮對海洛因依賴者抗复吸的治療作用探討	中國臨床康复, 2001 Nov, 5(11), 117
蘇木金,劉華承,王立公,李立凱,陳偉明,劉靜飛	2001a	海洛因依賴脫毒后康复期使用納曲酮防止复吸附77例一年隨訪觀察	中國藥物濫用防治雜志, 2001, 30(1), 16-8
蘇木金,譚國生,梁劍芳,王愛蘭,王以秀	2001b	小劑量納曲酮結合行爲心理干預和家庭介入防复吸效果	中國藥物依賴性雜志, 2001, 10(2), 121-3
楊治平	2000	海洛因依賴者脫毒后納曲酮干預复吸隨訪5例	中國藥物依賴性雜志, 2000, 9(4), 262-4

Author(s)	Year	Title	Source
丰麗萍	2000	納曲酮對防治海洛因脫毒后复吸的作用	現代中西醫結合雜志, 2000 May, 9(9), 808-9
楊征，江孝春，李樺等	1999	國產鹽酸納曲酮人體耐受性試驗	中國臨床藥理學雜誌, 15: 187-90
李東俊,梁爾軍	1999	國產鹽酸納曲酮預防海洛因脫毒后复吸的雙盲對照研究	中國藥物濫用防治雜志, 1999, 第1期
姜佐宁,郭崧,湯宜朗,牛光胜	1999	鹽酸納曲酮對阿片類成癮脫毒后防止复發效能的再評价-1088例納曲酮維持治療臨床研究.	中國藥物依賴性雜志, 1999, 8(4)
秦伯益	1999	納曲酮使用中的問題和經驗	中國藥物濫用防治雜志, 1999, 第2期
梁素英	1999	納曲酮用于海洛因脫毒后預防复吸46例	四川精神衛生, 1999, 第1期
潘偉業,邵曉芬	1999	納曲酮對海洛因依賴戒斷后的抗复吸作用	臨床精神醫學雜志, 1999, 第5期
蔣忠亮	1999	納曲酮用于阿片類藥物依賴者抗复吸治療的結果分析	中國藥物依賴性雜志, 1999, 8(2)
鄭洪波,陳國強,黃遠光,周亮,鄧子雄,任浩強	1999	鹽酸納曲酮對阿片類依賴脫毒后維持治療的臨床觀察	中國神經精神疾病雜志, 1999, 第5期
卓福鎮,張云,許瑞榮,朱計芬,袁德發	1998	國產鹽酸納曲酮用于海洛因依賴脫毒后預防复吸142例分析	中國藥物濫用防治雜志, 1998, 第6期
姜佐宁,郭松,吳艷梅,楊征,劉岳彪,蘇木金,劉華承,沙麗君,張滇民,羅曉云,楊介文,卓福鎮,許瑞榮,梁爾軍,李東俊,陳國強,馬崔	1998	鹽酸納曲酮用于阿片類依賴者脫毒后預防复發的效能研究	中國藥物依賴性雜志, 1998 Feb, 7(1)
張銳敏	1998	路脫菲及納曲酮用于海洛因依賴者家庭戒毒治療模式的探討	中國藥物依賴性雜志, 1998 May, 7(2)
楊曉松,王永崇,朱光榮,景風標,毛超,楊洁,李云飛	1998	鹽酸納曲酮防复吸初步研究	中國藥物依賴性雜志, 1998 Aug, 7(3)
羅曉云	1998	鹽酸納曲酮——海洛因依賴脫毒后防复吸輔助治療藥物	中國藥物濫用防治雜志, 1998, 第2期

Author(s)	Year	Title	Source
--	1997	戒毒領域防复吸的輔助良藥——鹽酸納曲酮片	中國藥物濫用防治雜志, 1997, 第3期
江玲芬,丁佩瑾,金偉麗,李文惠	1997	東莨菪鹼聯合納曲酮治療海洛因成癮的臨床觀察	宁波醫學, 1997, 第5期
梁爾軍，李東俊，姜漱玉，王興星，曹長安，張建軍，占德文	1997	國產鹽酸納曲酮用于阿片類脫毒后預防复吸效能的研究	中國藥物濫用防治雜志, 1997, 第2期
梁爾軍,李東俊,姜漱玉,王興星,曹長安,張建軍,占德文	1997	鹽酸納曲酮用于阿片類成癮脫毒后預防复吸效能的雙盲對照研究	中國藥理學与毒理學雜志, 1997, 第2期
楊征,趙立權,江孝香,玉安,蔡月芳,徐志明,盧小兵,顧軍	1997	國產鹽酸納曲酮對阿片類依賴脫毒治療后預防复吸的療效觀察	中國藥物依賴性雜志, 1997, 第2 期
江孝香，龐雪艷，楊征	1997	納曲酮Ⅰ期臨床試驗的組織管理及護理	中國藥物濫用防治雜志, 1997, 第3期
李婷，陳國強	1997	國產鹽酸納曲酮用于海洛因依賴者脫毒后預防复吸效能的雙盲對照研究	中國藥物濫用防治雜志, 1997, 第1期
沙麗君,程琳霞,張志祥,劉澤源	1997	納曲酮預防海洛因癮戒斷后复吸	中國新藥与臨床雜志, 1997, 第6期
陸蘇南	1997	丁丙諾啡的Ⅱ期臨床試驗:脫毒治療及后續的納曲酮治療	中國藥物依賴性雜志, 1997, 第4 期
楊征，劉岳彪，趙立權，江孝香，衛玉安，蔡月芳，盧小兵，顧軍	1997	國產鹽酸納曲酮對阿片類依賴脫毒治療后預防复吸的療效觀察	中國藥物濫用防治雜志, 1997, 第2期
羅曉云,楊介文,曹金蘭,牛冠英,康玉蘭	1997	美沙酮、丁丙諾啡、可樂定、納曲酮“階梯式”療法治療海洛因依賴脫毒后复吸患者33例	中國藥物依賴性雜志, 1997, 第3期
蘇木金,劉華承,鄧忭明,王立功,董小岩	1997	海洛因癮康复期使用納曲酮防止复吸100例	中國新藥与臨床雜志, 1997, 第3期
王小鐵，秦伯益	1995	納曲酮防止阿片類依賴病人戒毒后复吸的研究現狀	中國藥物依賴性雜志, 1995, 第3期

Appendix III: News from Australia: Suicides, Overdoses Linked to Naltrexone

Source: Courier-Mail, The (Australia)

Contact: cmletters@qnp.newsltd.com.au
Website: http://www.thecouriermail.com.au/
Details: http://www.mapinc.org/media/98
Authors: Catriona Mathewson, Sean Parnell

SUICIDES, OVERDOSES LINKED TO DETOX DRUG

A CONFIDENTIAL briefing paper on national trials of the heroin detoxification drug naltrexone has revealed alarming rates of overdose and suicide among those receiving treatment.

The paper, prepared for Queensland Health Minister Wendy Edmond by senior health bureaucrat Dr Alun Richards, contains details of a draft report on the trials.

Queensland participated in the trials of oral naltrexone treatment and submitted results to the National Drug and Alcohol Research Centre, which will officially release its findings next month.

Details of the research came yesterday as the Medical Board continued its investigation into Brisbane doctor Stuart Reece's use of controversial naltrexone implants.

Premier Peter Beattie issued a veiled attack on federal health authorities for not probing the unauthorised use of implants before his Government initiated the Medical Board investigation.

Mr Beattie, who conceded he had not been fully briefed on the investigation, said there were "difficulties" in the relationship between state and federal health authorities.

But he said the implants were only approved for trial purposes in Perth, and had federal health authorities prevented the implants being used in Queensland the investigation "would never have happened."

"I understand there are emotional issues involved and I understand the role of the Medical Board," Mr Beattie said.

"But if the Medical Board wasn't moving to protect lives, then everyone . . . would be belting the Government, and quite rightly."

A Therapeutic Goods Administration spokeswoman yesterday refused to detail any investigation into the implants, whether importation would be restricted or whether an application had been made to allow their use in Australia.

Board president Dr Lloyd Toft said yesterday it was hoped the investigation into Dr Reece would be completed within two months.

While Dr Reece has been banned from using naltrexone implants, he may still prescribe oral naltrexone, which has been evaluated in the trials.

The confidential briefing paper shows the trials found naltrexone detoxification was widely associated with a higher death rate than other methods of treatment.

However, it did concede that naltrexone showed good results when patients continued taking the drug, with Dr Richards stating: "Where patients have died after using naltrexone it is usually because they have stopped taking the drug and have reverted to using heroin."

The paper stated that national trial results showed naltrexone treatment was associated with a heroin overdose rate (both fatal and non-fatal) of 46.3 per 1000, against a rate of 2.2 non-fatal overdoses per 1000 for methadone. Four out of 454 patients on naltrexone died during the study.

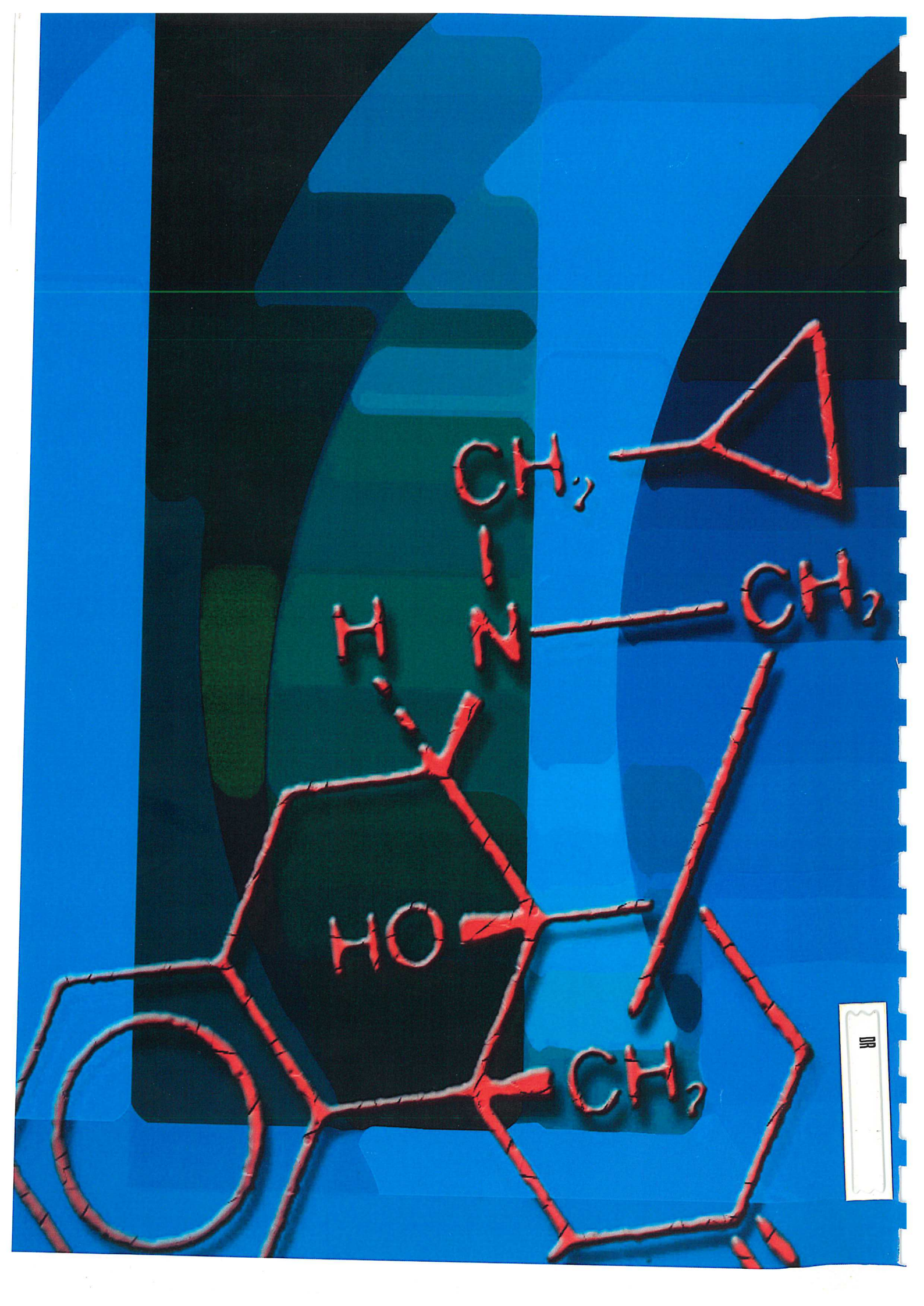
It also found the highest rate of "suicide-related events" (6.6 per 1000 patients) with naltrexone

Appendix IV: Expenditure of the Project

Expenditure Item	Description	Amount $
Personal Emoluments	Salary & MPF for Research Staff	701,840
Expenses for Medications and Clinical Trial	Naltrexone	127,600
	Medications Preparation and Consultation Fees[7]	20,000
	Compensation fee for Participants	400
	Laboratory Back-up	660
Accountant Fee		2,500
Sub-total		853,000
University Overhead	15%	127,950
TOTAL		**980,950**

[7] The School of Pharmacy of the CUHK had provided support in the randomization process and preparation for the medications. The charge was to cover the expenses on technical support, consumables and professional consultation.

BDF-010025 project


CH2
H
N
CH2
HO
CH2