

Methadone maintenance treatment in Spain: the success of a harm reduction approach

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Problem During the 1980s, Spain had very strict laws limiting access to opioid agonist maintenance treatment (OAMT). Because of this, mortality among people who used illicit opioids and other illicit drugs was high. Spain was also the European country with the highest number of cases of acquired immunodeficiency syndrome transmitted through illicit drug injection.

Approach The rapid spread of human immunodeficiency virus (HIV) infection among people using heroin led to a shift from a drug-free approach to the treatment of opioid dependence to one focused on harm reduction. A substantial change in legislation made it possible to meet public health needs and offer OAMT as part of harm reduction programmes in the public health system, including prisons.

Local setting Legislative changes were made throughout the country, although at a different pace in different regions.

Relevant changes Legal changes facilitated the expansion of OAMT, which has achieved a coverage of 60%. A parallel reduction in the annual incidence of HIV infection has been reported. Reductions in morbidity and mortality and improved health-related quality of life have been described in patients undergoing OAMT.

Lessons learnt The treatment of opioid dependence has been more heavily influenced by moral concepts and prejudices that hinder legislation and interfere with the implementation of OAMT than by scientific evidence. To fulfil public health needs, OAMT should be integrated in harm reduction programmes offered primarily in public facilities, including prisons. Longitudinal studies are needed to detect unmet needs and evaluate programme impact and suitability.

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Introduction

The epidemic of dependence on illicit drugs, especially heroin, began in Spain in the late 1970s. By 1980, the incidence of heroin use had peaked.¹ In addition, the epidemic of human immunodeficiency virus (HIV) infection started in the 1980s. According to estimates, Spain reached its highest incidence of HIV infection related to the injection of illicit drugs in 1984: 79 cases per 100 000 inhabitants.² During the early 1980s, the network for dependence on illicit drugs had not been developed yet and therapy consisted mainly in sending patients to drug-free programmes or to residential rehabilitation facilities promoting abstinence and managed by people who were not health professionals.³ Although physicians were allowed to prescribe methadone for heroin dependence,⁴ treatment was available mainly in the private sector. As of 1985, only around 5000 patients were on methadone maintenance treatment (MMT) in Spain (Fig. 1).

In 1985, the establishment of the National Plan on Drugs hastened the development of a network for the treatment of opioid dependence. At that time a drug-free approach still prevailed, but in 1985 a new ministerial order abolished the private prescription of methadone.⁴ The drug, which was the only opioid agonist that could be used to treat heroin dependence, had to be prescribed in specially-licensed prescription centres by physicians in the public sector. These centres were designated exclusively for the administration of MMT. The new legislation surrounding MMT established a maximum daily methadone dose of 40 mg, made it obligatory to perform weekly urinalyses to detect illegal concurrent use of illicit drugs and mandated forced discharge from MMT when

urinalyses gave positive results in a given patient after three months in treatment. Methadone dispensing centres were very few and waiting lists of more than 12 months were the norm. The policy on MMT was so restrictive that by 1987 only 1000 patients were still on MMT (Fig. 1). Programmes that followed a drug-free approach and provided treatment with naltrexone were practically the only ones available, despite their low client retention rates.⁶ At the same time, the National Register of AIDS Cases showed that by the end of 1993, 14 479 AIDS cases had been diagnosed among people injecting heroin. This represented 64% of all AIDS cases diagnosed in Spain at the time and Spain was the European country with the largest number of AIDS cases related to the injection of illicit drugs.⁷

The objective of this paper is to describe the influence of Spanish laws surrounding OAMT on the health of people dependent on heroin, including HIV infection rates among them.

Approach

The great spread of HIV infection brought about substantial changes in the laws surrounding the prescription and dispensation of methadone in Spain.⁴ With the new law in 1990, the approach to the treatment of heroin dependence changed; a drug-free approach gave way to one focused on harm reduction. OAMT for opioid dependence was available in specially-licensed public or non-profit centres, including prisons, with full or partial public support. Centres rather than individual professionals were licensed to both prescribe and dispense OAMT and only physicians working in the special centres could order this treatment. Methadone was practically the only drug used in OAMT. The criteria for admission to treat-

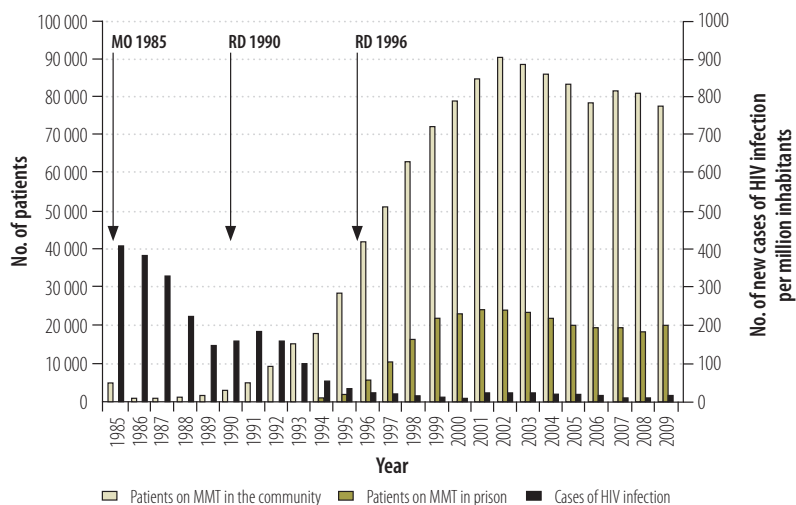
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(Submitted: 1 August 2012 – Revised version received: 24 October 2012 – Accepted: 4 December 2012)

Fig. 1. Patients on methadone maintenance treatment (MMT) in Spain, both in the community (1985–2009) and in prison (1992–2009), with reference to legislation and new cases of HIV infection related to illicit drug injection per million population



HIV, human immunodeficiency virus; MO, ministerial order; RD, royal decree.

The data were obtained from the Delegación del Gobierno para el Plan Nacional Sobre Drogas and Barrio G et al.^{3,10,11}

ment included: (i) a diagnosis of opioid dependence; (ii) a history of drug-free treatment (except for pregnant women and HIV-infected individuals). There were no restrictions on methadone dosage or length of treatment.

The last change in legislation, in 1996, made a diagnosis of opioid dependence the only requirement for enrolment in OAMT.⁴ Apart from public centres, physicians in private practice and pharmacies could also be licensed to prescribe and dispense methadone.⁴

Centre characteristics

Although the law of 1996 authorized the use of different opioid agonists in OAMT, oral methadone has been by far the one most frequently prescribed.⁴ Methadone is available in all regions of Spain, mainly in the public health system (free of charge) but also in private practice. The distribution and organization of MMT centres differs by region. Centres involved in methadone treatment can be classified according to their particular activity: prescribing and dispensing, dispensing only or prescribing only. Prescribing and dispensing centres perform a variety of treatment-related activities, from prescribing the drug to fixing dosing and treatment duration, performing periodic urinalyses, providing counselling services and dispensing the drug. Centres that only prescribe are also involved in most of the aforementioned activities, but they do not

dispense methadone. Centres that only dispense do nothing more than provide patients with their dose of methadone. Most centres that prescribe only and that prescribe as well as dispense are located in specific services that also offer treatments for dependence on drugs other than opioids, such as cocaine or sedatives, and alcohol abuse. Methadone could be dispensed in drug dependence centres, primary health centres, mental health facilities, prisons and pharmacies. Most centres that only dispense methadone are located in primary health-care services.

OAMT in Spain is characterized by the following: (i) a diagnosis of opioid dependence is the only eligibility criterion; (ii) opioid dosage is individualized according to a patient's clinical course, without any upper limit; (iii) treatment is as long as needed and long-term OAMT is encouraged; (iv) a take-home policy is highly recommended and decisions are made individually, on clinical grounds; (v) in most centres, violence, consumption and trafficking in the centre are the only criteria for forced discharge, in which case centre staff make efforts to transfer the patient to another treatment centre for continuation of OAMT; (vi) suspension of OAMT is decided by agreement among centre team members and the patient in accordance with personal and social considerations and clinical parameters.

Most of the centres involved in OAMT treatment also provide screening for HIV infection, hepatitis C virus infection, hepatitis B virus (HBV) infection and tuberculosis, as well as HBV vaccination. They also supervise daily treatment for these conditions if needed. Combination treatment with buprenorphine and naloxone has been authorized in Spain since 2008 and was included in the public health system in 2010. Unlike methadone, buprenorphine and naloxone can be purchased with a prescription in any pharmacy.

Methadone maintenance treatment in prisons

People dependent on heroin who were not on OAMT often had trouble with the law and more and more were being incarcerated. The law passed in 1990 included a paragraph on the use of methadone in prisons⁴ and, since December 1999, MMT has been available in almost all prisons. This makes it possible for inmates to start or continue MMT and to continue treatment in a community programme after being released.

Changes observed

Opioid agonist maintenance treatment

Regional differences in health service structure led to considerable diversity in the structural characteristics of OAMT networks. In 1994, 224 of the 280 centres providing MMT in Spain were assessed. A total of 13 402 patients were receiving MMT in the study centres; they had a mean age of 29 years, 79% were males and about 60% were HIV-positive. The proportion of the population on MMT varied by region (mean: 6.7 patients in MMT per 10 000 inhabitants; range: 0.9–15.8).⁸

After the change in legislation that took place in 1996, another study⁹ reported a large increase in the number of MMT patients, a 125% increase in methadone centres, and a significant increase in the availability of MMT in prisons (Fig. 1). According to data for 1992, 90 prisoners were enrolled in MMT¹⁰ and the number increased progressively until 2001, when 24 304 patients were enrolled in MMT. Since then, the number has decreased from 24 015 in 2002 to 20 055 in 2009 (Fig. 1).¹¹

The laws surrounding MMT have remained unchanged in Spain since

Box 1. Summary of main lessons learnt

- Moral concepts and prejudices that hinder legislation and interfere with the implementation of OAMT have been more influential in the treatment of opioid dependence than the scientific evidence.
- To attend public health needs, OAMT should be integrated in harm reduction programmes, primarily in prisons and other public facilities.
- Longitudinal studies are needed to detect unmet needs and evaluate the impact and suitability of OAMT interventions.

OAMT, opioid agonist maintenance treatment.

1996. In 2007, a progressive increase in the number of patients on MMT began to occur and peaked at 81 706 the same year, and a slow downward trend began after that (Fig. 1). Changes in legislation in 1990 and 1996, previously described, and the parallel expansion of OAMT produced a rise in OAMT coverage from 21% in 1996 to 43% in 1999. By 2010 OAMT coverage had reached 60%.⁵ Some longitudinal studies have been performed; one of them showed that retention within MMT programmes was 72% after 44 months in treatment.¹²

Impact on mortality and morbidity

A decrease in mortality associated with MMT has been demonstrated in a cohort study;¹³ the main factor associated with overdose mortality was not being in MMT at the time of death. Also, MMT influenced AIDS related mortality. In this study, overall mortality decreased from 59 deaths per 1000 person-years in 1992 to 16 in 1999.¹³ A steady decrease in the number of new HIV cases related to illicit drug injection was observed (Fig. 1).⁵

Impact on quality of life

The availability of OAMT has led to an improvement in health-related quality of life for people dependent on illicit heroin. One study showed that this improvement was substantial after only 30 days of treatment and throughout the follow-up period in patients on MMT who were observed for a period of 3 years.¹⁴

Discussion

Since 1999, Spain has been one of the countries with the highest levels of OAMT coverage in the world.¹⁵ Estimates show that in the European Union, about half of the people who are dependent on illicit opioids have access to MMT. Coverage figures are comparable to those reported in Australia and

the United States of America and higher than figures from Canada, China and the Russian Federation (where OAMT has not been introduced yet). Coverage of the target population varies between European countries. It is over 60% in Luxembourg, Malta and Spain; 40–60% in Austria, Finland, Germany, Ireland, Italy, the Netherlands and Norway; 30–40% in the Czech Republic and Hungary; and less than 30% in Cyprus, Greece, Lithuania, Poland and Slovakia.^{5,16} Methadone is the most commonly prescribed opioid agonist in Europe; it is used in 75% of patients on OAMT. Overall buprenorphine is the second most commonly used opioid agonist, although it is the one most often used as opioid maintenance treatment in Croatia, Cyprus, the Czech Republic, Finland, France and Sweden. Other opioid agonists are available in some countries: slow-release morphine in Austria, Bulgaria, Slovakia and Slovenia; codeine in Cyprus and Germany, and diacetylmorphine in Belgium, Denmark, Germany, the Netherlands, Spain and the United Kingdom of Great Britain and Northern Ireland. However, these represent only a small proportion of the treatments used. Financing of OAMT varies between European countries. Lack of public funding is the main obstacle to their expansion in countries such as Bulgaria and Poland.¹⁷

In Spain, public opinion surrounding OAMT has been regularly evaluated since 1995. About 66% of the general population is in favour of methadone treatment for opioid dependence and nearly 50% favours the medical use of heroin.¹⁸

Preventing the spread of HIV infection takes more than OAMT; it also depends on other harm reduction strategies, such as the establishment of needle and syringe programmes and supervised injection centres, free distribution of condoms and provision of highly-active antiretroviral therapy (HAART) to reduce viral load in HIV-positive individuals, and hence the risk

of viral transmission. In Spain, syringe provision started in 1989 and was very low until 1995, but it increased considerably during 1995–1999, stabilized in 1999–2004 and then decreased again. However, longitudinal analyses show that moderate coverage (i.e. 100–200 syringes per injected opioid user or 20–40% of users) was reached by 2000, but high levels (i.e. > 200 syringes per user or > 40% of users) had not been reached yet in 2010.⁵ The first supervised injection centre in Spain became operative in Madrid in 2000; in 2002 a second one became operative in Barcelona, where seven such centres were active by 2012. HAART has been widely available free of charge for all HIV-positive people in Spain since late 1996. Its use has been associated with a reduction in progression to AIDS and in AIDS-related mortality.¹³

Future directions in Spain

After an epidemic of dependence on illicit drugs, especially heroin, that has lasted for more than 30 years, Spain has learned several important lessons to do with efforts to reduce the morbidity and mortality associated with drug dependence (Box 1). In future, several actions will be required to continue to address this problem in Spain. Some of the most important ones will be the provision of OAMT, needle and syringe exchange programmes, supervised injection, condom dispensation and vaccination against hepatitis B in treatment facilities for people dependent on injected opioids. Just as important will be recognizing the need to diagnose and treat psychiatric comorbidity in patients dependent on illicit drugs and offering them integrated, or at least parallel, treatment in networks for drug dependence and mental health networks. However, the effects of the current economic crisis are unpredictable. When this paper was written, methadone treatment was still government-funded, but a worsening of the crisis could result in decreased public funding and a change in epidemiologic trends in the use of injected opioids. ■

Acknowledgements

We thank Paola Rossi for her valuable comments. Our work was supported by Fondo de Investigaciones Sanitarias, Instituto Carlos III (RD06/0001/1009).

Competing interests: None declared.

ملخص

العلاج الصياني بالميثادون في إسبانيا: نجاح أسلوب الحد من الأضرار

الرغم من اختلاف وتيرتها في الأقاليم المختلفة. التغييرات ذات الصلة بسرت التغييرات القانونية توسيع العلاج الصياني بناهض المواد الأفيونية المفعول، الذي حقق تغطية بنسبة 60٪. وتم الإبلاغ عن انخفاض مواز في الحدوث السنوي لعدوى فيروس العوز المناعي البشري. وتم وصف الانخفاضات في معدلات الأمراض والوفيات وتحسين نوعية الحياة المرتبطة بالصحة لدى المرضى الذين يخضعون للعلاج الصياني بناهض المواد الأفيونية المفعول.

الدروس المستفادة تأثر العلاج بالاعتماد على المواد الأفيونية المفعول بشدة بالمفاهيم الأخلاقية وأوجه الإجحاف التي تعوق التشريعات وتتعارض مع تنفيذ العلاج الصياني بناهض المواد الأفيونية المفعول مقارنة بتأثره بالبيئات العلمية. ولتلبية احتياجات الصحة العمومية، ينبغي دمج العلاج الصياني بناهض المواد الأفيونية المفعول في برامج الحد من الأضرار المقدمة بشكل رئيسي في المرافق العمومية، بما في ذلك السجون. ولابد من إجراء دراسات طويلة لكشف الاحتياجات غير الملباة وتقييم أثر البرامج ومدى ملاءمتها.

المشكلة خلال ثمانينيات القرن العشرين، وضعت إسبانيا قوانين بالغة الصرامة تحد من إتاحة العلاج الصياني بناهض المواد الأفيونية المفعول (OAMT). ونظراً لهذا، كان معدل الوفيات بين الأشخاص الذين استخدموا المواد الأفيونية المفعول غير المشروعة وغيرها من الأدوية غير المشروعة مرتفعاً. وكانت إسبانيا أيضاً البلد الأوروبي الذي يوجد به أعلى عدد من حالات الإصابة بمتلازمة العوز المناعي المكتسب التي يتم نقلها من خلال حقن الأدوية غير المشروعة.

الأسلوب أدى الانتشار السريع لعدوى فيروس العوز المناعي البشري (HIV) بين الأشخاص الذين يستخدمون الهيروين إلى التحول من أسلوب خال من الأدوية للعلاج المعتمد على المواد الأفيونية المفعول إلى أسلوب يركز على الحد من الأضرار. وبفضل تغيير كبير في التشريعات، تحققت تلبية احتياجات الصحة العمومية وتقديم العلاج الصياني بناهض المواد الأفيونية المفعول كجزء من برامج الحد من الأضرار في نظام الصحة العمومية، بما في ذلك السجون.

المواقع المحلية تم إدخال تغييرات تشريعية في أنحاء البلد، على

摘要

西班牙美沙酮维持治疗：减少伤害方法的成功

问题 在20世纪80年代，西班牙的法律非常严格地限制使用阿片受体激动剂维持治疗（OAMT）。因此，使用非法阿片类药物和其他非法毒品的人的死亡率很高。西班牙也是通过非法毒品注射感染艾滋病的病例数量最多的欧洲国家。

方法 艾滋病毒（HIV）感染在使用海洛因的人群中迅速蔓延，导致阿片类药物依赖无毒治疗方法转变为以减少伤害为主的治疗。立法上的重大变革使我们能够满足公共健康需求，并在包括监狱在内的公共卫生系统中提供OAMT作为减少伤害方案的一部分。

当地状况 尽管各地步调不一，但是在全国各地都有立法的变革。

相关变化 法律变革促进OAMT的推广，实现了60%的覆盖率。据报告，HIV感染的年发病率也同步降低。在接受OAMT治疗的患者中也有发病率和死亡率减少以及健康相关生活质量改善的报告。

经验教训 道德观念和偏见对阿片类药物依赖治疗的严重影响比科学证据更大，它们阻碍了立法并干扰了OAMT的实施。要满足公众的卫生需求，应将OAMT纳入主要由公共设施（包括监狱）提供的减少伤害方案中。需要进行纵向研究以发现未满足的需求，并评估方案的影响和适用性。

Résumé

Traitement de maintien à la méthadone en Espagne: le succès d'une approche par réduction des risques

Problème Dans les années 1980, l'Espagne avait des lois très strictes limitant l'accès au traitement de maintien par agoniste des opioïdes (TMAO). Pour cette raison, la mortalité parmi les utilisateurs d'opioïdes illicites et autres drogues illégales était élevée. L'Espagne était également le pays européen présentant le plus grand nombre de cas de syndrome d'immunodéficience acquise transmis par injection de drogues illicites.

Approche La propagation rapide du virus de l'immunodéficience humaine (VIH) chez les personnes consommant de l'héroïne a mené au basculement d'une approche non médicalisée du traitement de la dépendance aux opiacés à une position axée sur la réduction des risques. Un changement important de la législation a permis de répondre aux besoins de santé publique et d'offrir un traitement de maintien par agoniste des opioïdes dans le cadre des programmes de réduction des risques dans les organismes de santé publique, y compris les prisons.

Environnement local Des modifications législatives ont été apportées dans tout le pays, bien qu'à un rythme différent selon les régions.

Changements significatifs Les adaptations juridiques ont facilité

le développement du traitement de maintien par agoniste des opioïdes, qui a atteint une couverture de 60%. Une réduction parallèle de l'incidence annuelle de l'infection par le VIH a été observée. Des réductions de morbidité et de mortalité ainsi qu'une amélioration de la qualité de vie liée à la santé ont été décrites chez les patients suivant un tel programme.

Leçons tirées Le traitement de la dépendance aux opiacés a été plus fortement influencé par des concepts moraux et les préjugés qui entravent la législation et interfèrent avec la mise en place de programmes de traitement que par des preuves scientifiques. Afin de répondre aux besoins de santé publique, des traitements de maintien par agoniste des opioïdes devaient être intégrés dans les programmes de réduction des risques, majoritairement proposés dans les lieux publics, y compris les prisons. Des études longitudinales sont nécessaires pour détecter les besoins non satisfaits et pour évaluer l'impact et la pertinence du programme.

Резюме

Метадоновая поддерживающая терапия в Испании: успешность стратегии по снижению вреда

Проблема В 1980-е годы в Испании действовали очень строгие законы, ограничивавшие доступ к поддерживающей терапии агонистами опиоидов (ПТАО). По этой причине смертность среди людей, которые потребляли запрещенные опиоиды и другие запрещенные наркотики, была высока. Испания также относилась к числу европейских государств с наибольшим числом случаев синдрома приобретенного иммунодефицита, передаваемого через внутривенное введение запрещенных наркотиков.

Подход Стремительное распространение инфекции вируса иммунодефицита человека (ВИЧ) среди людей, потребляющих героин, привело к замене немедикаментозного подхода к лечению опиоидной зависимости методом, ориентированным на снижение вреда. Существенное изменение законодательства позволило удовлетворить требования общественного здравоохранения и предложить ПТАО в рамках программ сокращения вреда в системе общественного здравоохранения включая тюрьмы.

Местные условия Изменение законодательства было проведено

по всей стране хоть и с разными темпами в разных регионах.

Осуществленные перемены Изменение законодательства упростило распространение ПТАО, охват которого достиг 60%. Одновременно отмечалось снижение числа новых случаев ВИЧ-инфекции в год. Сокращения заболеваемости и смертности, а также улучшение качества жизни, обусловленное здоровьем, отмечены у пациентов, получавших ПТАО.

Выводы На лечение опиоидной зависимости наибольшее влияние оказывают не научные доказательства, а моральная концепция и предубеждения, которые затрудняют изменение законодательства и препятствуют внедрению ПТАО. Для удовлетворения требований общественного здравоохранения требуется внедрение ПТАО в программы сокращения вреда, предлагаемые преимущественно в государственных учреждениях включая тюрьмы. Длительные повторные исследования необходимы для определения неудовлетворенных потребностей, а также оценки влияния программы и ее пригодности.

Resumen

El tratamiento de mantenimiento con metadona en España: el éxito de un enfoque dirigido a la reducción de daños

Situación Durante la década de los años 80, las estrictas leyes en España limitaban en acceso al tratamiento de mantenimiento con opioides agonistas, por lo que la mortalidad entre los consumidores de opiáceos y otras drogas ilegales era elevada. España era el país europeo con el mayor número de casos de síndrome de la inmunodeficiencia adquirida transmitidos por la inyección de drogas ilegales.

Enfoque La rápida propagación de la infección por el virus de la inmunodeficiencia humana (VIH) entre personas que consumían heroína ocasionó un cambio de un enfoque sin fármacos para el tratamiento de la dependencia de opiáceos a otro dirigido a la reducción de daños. Un cambio importante en la legislación permitió satisfacer las necesidades de salud pública y ofrecer el tratamiento de mantenimiento con opioides agonistas como parte de los programas de reducción de daños en el sistema de salud pública, incluidas las prisiones.

Marco regional Se realizaron cambios legislativos en todo el país, aunque a un ritmo distinto en las diferentes regiones.

Cambios importantes Los cambios legales facilitaron la expansión

del tratamiento de mantenimiento con opioides agonistas, que alcanzó una cobertura del 60 %. Se ha constatado una reducción paralela de la incidencia de la infección por el VIH, y se ha evidenciado una disminución de la morbilidad y la mortalidad, así como una mejora en la calidad de vida entre los pacientes que se someten al tratamiento de mantenimiento con opioides agonistas.

Lecciones aprendidas El tratamiento de la dependencia de opiáceos ha estado más influido por conceptos y prejuicios morales que dificultan la legislación e interfieren en la puesta en marcha del tratamiento de mantenimiento con opioides agonistas que por las pruebas científicas. A fin de cumplir con las necesidades de salud pública, se debería integrar el tratamiento de mantenimiento con opioides agonistas en los programas de reducción de daños ofrecidos en centros públicos, incluidas las prisiones. Es necesario realizar estudios longitudinales para detectar las necesidades insatisfechas y evaluar el impacto e idoneidad del programa.

References

1. Sánchez-Niubò A, Fortiana J, Barrio G, Suelves JM, Correa JF, Domingo-Salvany A. Problematic heroin use incidence trends in Spain. *Addiction* 2009;104:248–55. doi:10.1111/j.1360-0443.2008.02451.x PMID:19149821
2. De la Fuente L, Bravo MJ, Barrio G, Parras F, Suárez M, Rodés A et al. Lessons from the history of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic among Spanish drug injectors. *Clin Infect Dis* 2003;37:S410–5. doi:10.1086/377562 PMID:14648456
3. Camí J, de Torres S, San L. Guidelines and criteria for the admission of heroin dependence in the general hospital. *Med Clin (Barc)* 1984;82:327–31. PMID:6371401
4. Torrens M. Spain. In: Casselman J, Meuwissen J, Opdebeeck A, editors. *The legal aspects of substitution treatment: an insight into nine EU countries*. Belgium: European Monitoring Centre for Drugs and Drug Addiction; 2003. pp. 61–9.
5. Barrio G, Bravo MJ, Brugal MT, Díez M, Regidor E, Belza MJ et al.; Itinere Working Group. Harm reduction interventions for drug injectors or heroin users in Spain: expanding coverage as the storm abates. *Addiction* 2012;107:1111–22. doi:10.1111/j.1360-0443.2011.03759.x PMID:22151686
6. García-Alonso F, Gutierrez M, San L, Bedate J, Forteza-Rei J, Rodríguez-Artalejo F et al.; Spanish Study Group in Drug Addiction. A multicentre study to introduce naltrexone for opiate dependence in Spain. *Drug Alcohol Depend* 1989;23:117–21. doi:10.1016/0376-8716(89)90016-1 PMID:2702921
7. Torrens M, Camí J. The effects of HIV infection on the development of methadone maintenance treatment in Spain. *Addiction* 1994;89:1707–8. PMID:7866257
8. Domingo-Salvany A, Pérez K, Torrens M, Bravo MJ, Antó JM, Alonso J. Methadone treatment in Spain, 1994. *Drug Alcohol Depend* 1999;56:61–6. doi:10.1016/S0376-8716(99)00011-3 PMID:10462094
9. Domingo-Salvany A. Los tratamientos de mantenimiento con metadona en España: análisis de los centros activos en 1997. In: *VI Encuentro Nacional sobre Drogodependencias y su Enfoque Comunitario, 3–5 November 1999, Cadiz, Spain*. Cadiz: Centro Provincial de Drogodependencias de Cádiz; 1999. [Spanish].
10. Plan Nacional sobre Drogas. *Memoria 1996*. Madrid: Delegación del Gobierno para el Plan Nacional Sobre Drogas, Ministerio del Interior; 1996. [Spanish].

11. Plan Nacional sobre Drogas. *Memoria 2009*. Madrid: Delegación del Gobierno para el Plan Nacional sobre Drogas, Ministerio del Interior; 2009. [Spanish].
12. Torrens M, Castillo C, Pérez-Solá V. Retention in a low-threshold methadone maintenance program. *Drug Alcohol Depend* 1996;41:55–9. doi:10.1016/0376-8716(96)01230-6 PMID:8793310
13. Brugal MT, Domingo-Salvany A, Puig R, Barrio G, García de Olalla P, de la Fuente L. Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction* 2005;100:981–9. doi:10.1111/j.1360-0443.2005.01089.x PMID:15955014
14. Torrens M, Domingo-Salvany A, Alonso J, Castillo C, San L. Methadone and quality of life. *Lancet* 1999;353:1101. doi:10.1016/S0140-6736(05)76462-X PMID:10199379
15. World Health Organization/United Nations Office on Drugs and Crime, Joint United Nations Programme on HIV/AIDS. *WHO, UNODC, UNAIDS Technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users*. Geneva: WHO, UNODC, UNAIDS; 2009. Available from: http://www.unodc.org/documents/hiv-aids/idu_target_setting_guide.pdf [accessed 8 December 2012].
16. European Monitoring Centre for Drugs and Drug Addiction [Internet]. Data: statistical bulletin 2011. Lisbon: EMCDDA; 2011. Available from: <http://www.emcdda.europa.eu/stats11> [accessed 8 December 2012].
17. European Monitoring Centre for Drugs and Drug Addiction. *Annual report 2011: the state of the drugs problems in Europe*. Lisbon: EMCDDA; 2011. Available from: http://www.emcdda.europa.eu/attachements.cfm/att_143743_EN_EMCCDDA_AR2011_EN.pdf [accessed 8 December 2012].
18. de Sanidad M, Sociales e Igualdad S. Plan Nacional sobre Drogas [Internet]. Consumo, percepciones y opiniones de la población ante las drogas.1.1 Encuesta Domiciliaria sobre Alcohol y Drogas en España (EDADES), 1959–1999. Madrid: MSSSI; 2009. Available from: http://www.pnsd.msc.es/Categoria2/observa/pdf/EDADES_2009.pdf [accessed 8 December 2012]. [Spanish].