Maintenance treatment with depot opioid antagonists in subcutaneous implants: an alternative in the treatment of opioid dependence

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Abstract
A report is presented of treatment of 156 patients (male 98%) with opioid dependence (ICD-10 criteria) using a maintenance programme with depot opioid antagonists (naltrexone) as subcutaneous implants, started after an outpatient rapid antagonization regimen. The retention index in the treatment was from 80% in the sixth month, and 65% after one year. The patients were followed-up for 1 year after discharge. For 6 months after discharge 55.4% were still returning for follow-up visits and 20.8% after 1 year, all of them remaining abstinent to opioids. It is concluded that the programme is safe for the patients and shows a better retention index than programmes using oral antagonists, with an improved compliance (negative urine analysis) compared to the latter.

Introduction
After overcoming the health-care pressure of the 1980s and 1990s, and with the implantation of a management network throughout Spain, care for patients with opioid dependence is carried out currently according to technical and scientific criteria1 which are fortunately far removed from the social–philosophical–moral approaches of past decades.

The growing acceptance of the fact that treatment criteria in all fields of medicine should be revised based on “evidence-based medicine” and the ever-increasing need to adapt treatment programmes to efficacy criteria has led to the acknowledgement2 that programmes for treatment of drug dependence should be carried out in the least restrictive context possible to ensure adequate compliance, i.e. in a setting allowing for safe and effective application of the therapeutic measures. In this context, and in the case of opioid dependence, the therapeutic approaches most widely used today are maintenance programmes with opioid agonists and antagonists.

The great disproportion seen3 in favour of programmes with agonists versus programmes with antagonists is not actually due to major advantages of the former, but rather to two significant limitations of the latter. First, before...
starting treatment with antagonists, adequate physical detoxification must be performed\(^4\) to ensure that opioid receptors are free of opioids before introducing the antagonist. While methadone in decreasing doses is still used widely for detoxification procedures, rapid and ultrarapid protocols including clonidine, opiate receptors and antagonists have been proposed.\(^5\) Owing to health-care pressures, this need has become a true bottleneck for access to such programmes. Secondly, programmes involving antagonists are attributed a lesser treatment retention, and retention is precisely the factor associated most intimately with treatment success.\(^6\)

Our team, in collaboration with the research group of the Stapleford Centre in London (UK), has developed a treatment programme which attempts to overcome these disadvantages. The programme, referred to as NIMROD (naltrexone implants and rapid opioid detoxification), consists of the application of a rapid outpatient antagonization regimen, followed by the placement of a subcutaneous naltrexone implant, combined with individual motivational orientation and cognitive–behavioral psychotherapy. The results are evaluated below.

**Sample, material and methods**

The study sample comprised the first 156 patients subjected to the protocol in our centre. Patients were recruited between September 1998 (the date when the programme was started) and October 2000, in order to ensure a follow-up period of 12 months after clinical discharge in all patients included in the study.

During the 25-month recruitment period, classical detoxification was carried out in another 464 patients, 284 of whom continued maintenance treatment with oral naltrexone (the drug was administered at the centre three times a week, and the same psychotherapy as for the NIMROD group was used). This group was used for comparison purposes in the evaluation of some aspects of the study.

**Inclusion criteria**

The following patient inclusion criteria were used:

- Outpatients with criteria of opioid dependence (ICD-10)
- Compliance with the requirements of the center for admission to treatment.
- No concomitant disease or conditions contraindicating treatment or making evaluation and follow-up difficult.
- Acceptance of the treatment protocol by signing an informed consent.

**State conditions contraindicating treatment**

- Pregnancy and lactation
- Alcohol dependence
- Myocardic angina
- Epilepsy
- Severe disturbances of the cardiac rhythm
- Chronic obstructive lung disease

**Evaluation instruments**

The results of the study were obtained from the review of the clinical histories of the patients, including supplemental tests (laboratory, etc.), and the evaluation and diagnostic instruments used, including: EuropASI,\(^7\) Gold scale,\(^8\) Mini International Neuropsychiatric Interview (MINI-plus),\(^9\) International Personality Disorders Examination (IPDE),\(^10\) and urine analysis (Triage\(^1\) Merck).

The efficacy criteria included treatment compliance, retention index and the time elapsed without opioid consumption (assessed objectively).

**Methods**

The results obtained were grouped into different databases in which extreme values or values with great deviation from the mean were checked, and the accuracy of all data from at least 10% of the cases included was verified. The database was considered to be valid when the percentage error was less than 0.5%. After tabulating the study results and applying quality control, the data were analysed using SPSS 9.0 statistical software.

The medication regimen used for rapid antagonization is summarized in Table 1, and is the one commonly used in our setting\(^11\) since 1998, when medication protocols incorporated octreotide, a structural analog of somatostatin which
has eliminated in practice the gastrointestinal problems that were previously very common. The treatment programme consists of maintenance treatment with naltrexone as a subcutaneous implant, associated to psychosocial support therapy, starting with an outpatient rapid antagonization regimen as detoxification method. The data obtained on psychophysical co-morbidity can be found in Table 2.

The treatment protocol was as follows.

Visit 1: Evaluation of programme demand and indication

- Objective documentation of consumption status
- Complete physical examination (mainly):
  - Pregnancy
  - Cardiopulmonary function
  - Gastrointestinal tract
  - Supplemental tests (laboratory, etc.)
- Explanation of the protocol to the patient and relative in charge
- Signature of informed consent
- Dispensing medication and written instructions to relative
- Performance of the outpatient rapid antagonization regimen at the patient’s home, under supervision by the relative in charge.

Visit 2 (after 24 hours):

- Patient re-evaluation (medication where applicable: for example if the patient vomits we use metoclopramide)
- Revision of supplemental test results

<table>
<thead>
<tr>
<th>Table 1. Rapid antagonization regimen</th>
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<tbody>
<tr>
<td><strong>Premedication (hour – 1)</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>First dose (hour 0)</td>
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<td></td>
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<td>Second dose (hour 0 + 45 min)</td>
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<tr>
<td>Third dose (hour 0 + 105 min)</td>
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<table>
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<tr>
<th>Table 2. Co-morbidity</th>
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<tbody>
<tr>
<td>Psychiatric</td>
</tr>
<tr>
<td>Personality disorders</td>
</tr>
<tr>
<td>Dissocial 37.5%</td>
</tr>
<tr>
<td>Impulsive 25%</td>
</tr>
<tr>
<td>Schizoid 2.08%</td>
</tr>
<tr>
<td>Mixed anxiety – depression disorder 39.5%</td>
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<tr>
<td>Panic disorder 18.75%</td>
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</table>

Visit 3 (after 48 hours):

- Control and inspection of surgical wound
- MINI-plus and IPDE
- Urine analysis for drugs, where applicable

Implant and procedures

The implant is a cylinder measuring 22 mm in length and 9 mm in diameter that contains 1 g of naltrexone blended with a small amount of magnesium stearate, and 10 mg of triamcinolone, mounted in a bevelled syringe (Fig. 1). Placement is simple:

- The area is first anesthetized (lower third of the anterolateral abdominal wall); we use
0.5% bupivacaine with epinephrine as vasoconstrictor.

- A first superficial incision is made with a scalpel (no more than 2 cm).
- Dissecting scissors are used to prepare a pocket for housing the naltrexone cylinder.
- The syringe with the implant is inserted into the pocket and the plunger depressed to position the implant, after which correct placement is checked.
- Finally, the pocket is closed with two internal reabsorbable stitches and three external silk stitches.

After the first 15 minutes, the implant typically maintains blood naltrexone levels of 1 ng/ml, thought to be the minimum level necessary for blockade\textsuperscript{12} for 6–7 weeks, and sometimes up to 10 weeks replacement is therefore recommended every 2 months, because we have seen a few patients whose implants lasted barely 4 weeks; we usually suggest that the second implant be not later than 5 weeks after the first and then every 6–8 weeks. The associated therapy is individualized and consists of cognitive–motivational orientation\textsuperscript{13} the programme is revised every 2 months and, based on patient evolution, a decision can be made concerning implant renewal, switching to oral naltrexone or discontinuation of the antagonist.

After the naltrexone treatment period, ranging from 9 months to 1 year depending on the patient, a follow-up programme was implemented without antagonists but with laboratory tests (drugs screening) at least every 3 months, before proposing clinical discharge. The mean number of implants in the sample patients before switching to the oral route was 2.3; three patients used five implants and two received six, refusing the oral route throughout the programme.

Following clinical discharge, a voluntary follow-up period of 1 year was proposed, involving laboratory control visits every 2 months.

**Results**

**Sample description**

The study sample comprised the first 156 patients subjected to the treatment protocol using subcutaneous naltrexone implants, started during outpatient rapid antagonization (NIMROD). The socio-demographic and consumption data of the patients are as follows: males 98%, 28.8 years old; with partner 75%; with stable work 83.3%; education level middle to technical 79.1%; with heroin 80.58%; methadone 6.08%; heroin and methadone 13.33%; consumption inhaled 85.4%; consumption injected 14.6%; duration of consumption 6.2%; time since last relapse 9.5 months; drug use 0.1–1 g 87.5% and 1 g 12.5%; and number of previous treatments, nine.

**Safety**

No clinical complications occurred in any of the 156 antagonization regimens performed. The

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*Figure 1. Implantation of a cylinder measuring 22 mm in length and 9 mm in diameter containing 1 g of naltrexone blended with a small amount of magnesium stearate, and 10 mg of triamcinolone, mounted in a bevelled syringe.*
“mild” score in the Gold scale was not exceeded in any case, and the mean patient score was 21.6 points. The whole sample completed detoxification and went on to the implant-based maintenance programme.

During the implant maintenance programme, seven allergic reactions occurred (dermatological reactions such as rush in the place of the implant); these were treated with topical corticosteroids. No changes were required in the implant programme. Implant removal was not required in any patient, even in three episodes of surgical wound infection that were treated with antibiotic therapy and wound cleaning, and resolved without complications.

Course
The patient course or evolution was assessed by three parameters: quantitative change in the addiction severity index; maintenance of opioid and other drug withdrawal; and treatment retention.

The data on addiction severity at the start of treatment are shown in Fig. 2 as the mean scores of the sample in the EuropASI. These scores evolved after 6 and 12 months, as can be seen in the figure. Although improvement occurred in all areas, except for alcohol consumption and occupation, the only statistically significant difference was seen in the drug area at both 6 months ($p = 0.05$) and 1 year ($p = 0.01$).

No statistically significant differences were found between the mean baseline EuropASI values of patients in the NIMROD programme and patients included in the oral maintenance programme started with the classical detoxification regimen, except in the occupational and support areas ($p = 0.05$) in favour of the NIMROD group. Changes in the EuropASI score during treatment show significant differences in the drug area after 1 year ($p = 0.01$) (Figure 3), and in the family area after 6 months ($p = 0.05$) and 1 year ($p = 0.05$), also favouring the NIMROD programme.

Throughout the treatment programme monthly urine analyses for drugs were performed in the patients, and the results obtained were always minor in the NIMROD group.

The treatment retention index was also greater in the study sample (80% at month 6, 65% after 1 year) than in the patients given oral treatment (42% at month 6, 17% after 1 year). The difference was also statistically significant ($p < 0.05$). It should be stressed that there were no expulsions in the NIMROD programme: all patients were discharged from treatment or requested discharge voluntarily for social, family or occupational reasons. In only four cases was the treatment modality modified, referring the patients to a therapeutic community, and in all cases this was due to family reasons unrelated to the treatment.

Of the 101 patients who completed the treatment programme (65% of those who started it), 56 (55.44%) returned for the proposed follow-up visits for 6 months, and 21 (20.79%) patients for the whole 1-year period. Negative opioid laboratory test findings were made in all of them.

Discussion
For a maintenance programme with antagonists, the type of prior detoxification is obviously a minor factor. However, starting the programme
with an ambulatory rapid antagonization regimen (as in our case) has a number of advantages. For the patient, the approach shortens the time between consumption and withdrawal with a minimal impact upon daily reality, and also allows for early psychotherapeutic intervention. It has been shown that a higher number of patients coming from an antagonization regimen continue subsequent interventions compared with patients undergoing classical detoxification.\textsuperscript{14,15}

It is beyond the scope of this study to discuss the safety or efficacy of ambulatory rapid antagonization regimens as detoxification methods, as this has been shown widely elsewhere.\textsuperscript{11,16} – \textsuperscript{18} However, mention should be made of two aspects relevant to the programme analysed here, which are derived directly from patient characteristics.

First, the fact that the efficacy of ambulatory rapid antagonization regimens is close to 100% makes them ideal for detoxification purposes in precisely those subjects who have made multiple previous attempts.\textsuperscript{11} Secondly, the fact that no discontinuity exists between detoxification and the dependence eradication programme reduces dropouts in this period\textsuperscript{19} and promotes compliance with subsequent treatment.\textsuperscript{11}

It should be stressed that patients perceive detoxification as convenient, as reflected by the low score in the Gold scale recorded in the study sample (21.6 points). Because these results cannot be attributed to low consumption by the patients, as their consumption data agree with those usually found in our setting\textsuperscript{20} this could be due to high patient motivation (particularly due to their social–family situation), which can reduce the perceived withdrawal symptoms,\textsuperscript{21} and to the serial use of octreotide in the antagonization regimen, which has been able to minimize the gastrointestinal symptoms, reported by patients as being most unpleasant during antagonization.\textsuperscript{11,18}

The lower retention index in these programmes is also a serious disadvantage, for it has been shown that the length of time during which the patient participates in a programme (of whatever kind) is the factor associated most significantly with its success.\textsuperscript{22} However, we do not think this lower retention to be attributable to user dissatisfaction with antagonist-based programmes. In some of the most recent studies evaluated, patient perceived satisfaction was very high,\textsuperscript{23} and the retention values were also considerably higher than expected (64.3\% after 6 months).\textsuperscript{24} In our study, the retention index was higher than in series treated with oral antagonists, and approached or even exceeded the performance of some studies involving maintenance treatment with agonists (80\% after 6 months, and 65\% after 1 year).\textsuperscript{25} Further advantages with respect to the latter treatment approach include the prompt and sustained negativization of urine analyses because, in some studies with agonists, positive results in 50\% of urine samples are still found 2 years after the start of the programme.\textsuperscript{26}

The use of depot formulations is by no means new in psychiatry,\textsuperscript{27} and has been shown repeatedly to improve patient compliance. In our case, such improved compliance is essential, for it

\begin{figure}
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\includegraphics[width=\textwidth]{figure3.png}
\caption{Positive urine analyses (NIMROD), $n = 156$; oral route, $n = 248$.}
\end{figure}
guarantees adequate antagonization. It prevents the risk of overdose resulting from accidental or deliberate consumption\textsuperscript{11} and allows for effective psychotherapy without the consequences (new reinforcement and psychic effects of the substances) of point relapses,\textsuperscript{28} while increasing treatment compliance.\textsuperscript{21} Two of these factors are of vital importance because, as discussed above, various studies\textsuperscript{22} have shown that the length of time the patient is included in a programme (regardless of its nature) and the use of psychotherapy integrated in the programme are the two factors related most closely to therapeutic success. The use of the type of implant inserted during this study virtually guarantees adequate blood naltrexone levels of at least 6 weeks and polylactate-based implants providing adequate levels for around 6 months are now in use.\textsuperscript{12} It should be remembered that the minimum dose for ensuring effective opioid blockade appears to be 1 ng/ml; in order to maintain this level, oral doses ranging from 50 to 100 ng/ml daily are required.\textsuperscript{29,30} The metabolic overload is therefore lower with implants when compared with the oral route. This is not a particularly important consideration, as oral naltrexone has been shown widely to be safe even in patients with liver disease,\textsuperscript{31} but it should also be taken into account when contemplating possible indications and contraindications of a drug of this type.

The NIMROD programme was found to be safe for our patients. There have been no serious complications in either the antagonization or maintenance phases (although the series is small), and dropouts occurring during the programme have not been related directly to the programme itself.

A factor of growing relevance when evaluating the “performance” of a therapeutic programme is the evolution of the addiction severity index.\textsuperscript{32} In our series, no significant differences were seen between the baseline values and those obtained in other studies reported.\textsuperscript{33,34} No differences were seen either in demographic characteristics, consumption or physical and psychiatric co-morbidity (except for an unusually low level of HIV seropositivity even by current standards). Our sample is therefore representative of the patients who seek medical help in our setting and we can discard the possibility of bias in our results due to patient selection, as all patients requesting inclusion were admitted to the programme.

The change in the different EuropASI areas over time was positive in all areas except for alcohol consumption, and the decrease in severity was greater in those areas dependent directly upon treatment, such as the drug consumption area and the medical and psychiatric area, in agreement with the findings of other studies.\textsuperscript{35} The programme can therefore be considered effective from an objective point of view.

There are few published references regarding the results of post-treatment follow-up, due probably to the difficulty of such evaluation.\textsuperscript{25,36–38} In our series, 55.44% of urine analyses were negative at 6 months after clinical discharge and 20.79% after 1 year. Both figures are the highest reported to date for antagonist-based programmes, in which the maintenance of abstinence was established using indirect or non-objective methods.\textsuperscript{39}

Despite initial doubts, maintenance treatments with agonists (mainly methadone) are currently among the most widely used treatment options for patients with opioid dependence.\textsuperscript{40} Moreover, they have clearly been useful as regards diffusion of the damage reduction policies which have made such a great contribution to arresting expansion of the HIV epidemic and other infectious diseases related to intravenous drug use.\textsuperscript{41}

Nevertheless, a number of aspects related to such treatment are currently controversial, such as whether methadone is actually the best agonist in view of its pharmacological profile;\textsuperscript{42} whether dosing every 24 hours is really adequate in all patients;\textsuperscript{43} the very high consumption of other substances among users;\textsuperscript{28} and, lately, even aspects so widely accepted as its indication in HIV patients, as it has been shown recently that its use increases HIV infectivity (at least in vitro) and HIV activation and replication in infected mononuclear cells (peripheral blood mononuclear cells, PBMC).\textsuperscript{44} Other controversial issues include its multiple interactions with the new antiretroviral drugs\textsuperscript{45} or its use in pregnant women, in view of the differences seen in the duration of neonatal withdrawal syndrome compared with treatments using partial agonists\textsuperscript{46} and antagonists.\textsuperscript{47,48}

In this context, taking into account the recommendations of the World Health Organization (WHO), American Psychiatric Association...
(APA) and Spanish Society of Psychiatrists (SSP), among other organizations, to apply treatment in the least restrictive setting possible\textsuperscript{6} so as to cause minimal interference with the life experience of the patients, and to perform adequate desensitization of the stimuli conditioned by consumption (for which these must be present, but no new positive reinforcements should occur), the only valid alternative to an agonist programme is a maintenance programme using antagonists.

Programmes with antagonists (naltrexone) have a number of advantages which make them highly useful in approaching opioid dependence. Some of these advantages are classically accepted, such as their few contraindications and side effects,\textsuperscript{49} their almost total lack of drug interactions\textsuperscript{50} (except with opioids, of course), and the fact that results are obtained in the short term.\textsuperscript{36} Other more recently identified advantages include the observation that the use of such treatments enhances the activity of new antiretroviral drugs at CD4 lymphocyte level,\textsuperscript{51} or prevents malformations, decreases the duration of the neonatal withdrawal syndrome and may promote fetal maturation in animals studies and in pregnant addicts following detoxification.\textsuperscript{48,52,53} This has led to reconsideration of the assignment to particular treatment models of certain patients, such as HIV-infected patients or pregnant women, traditionally considered eligible for maintenance with agonists.

However, naltrexone has been relegated to second place (at least with regard to the number of treatments) due to three disadvantages which have been attributed to its use. First, before starting treatment with antagonists, physical detoxification of the patient is required.\textsuperscript{5} Secondly, antagonist maintenance programmes generally seem to receive less acceptance among patients, which in turn leads to a lesser treatment retention index than agonist-based programmes.\textsuperscript{4} The need for prior detoxification is a significant limitation, considering the saturation found in many hospital detoxification units and the poor performance of outpatient detoxification (although the advent of rapid and ultra-rapid regimens is quickly changing this situation),\textsuperscript{54} which often makes the need for detoxification a true “bottleneck” for the start of treatment.

Conclusions
1. The NIMROD programme was safe for our patients.
2. The maintenance programme with depot antagonists showed a greater retention index than programmes using oral antagonists.
3. Withdrawal was achieved in a shorter period of time, and the relapse-free interval was maintained for longer than in programmes using conventional antagonists.
4. Further longer-term studies, particularly of a comparative nature, are warranted to confirm the probable increased efficacy of this method.

References
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