

Opioid* Substitution Treatment (OST): A French/Portuguese Lesson for Norway and Others

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Abstract

Opioid dependency is a chronic relapsing disease, with danger of overdose when the tolerance is lost. What is optimal handling in a mess of confusing factors? I have found clues to this from the annual reports on drug issues of the European Union (EU) with its 28 member countries – from their drug addiction agency (EMCDDA), based in Lisbon, Portugal. Norway has a costly opioid substitution treatment (OST) program with very high drug related death (DRD) rate, and due to my personal experience as a general practitioner (GP), I have been curious to find out why this is the case. I have elaborated EU statistics on DRD, in order to compare trends, related to populations and the type of OST in 20 out of 28 EU countries. I have included non-member Norway, which also reports drug statistics to EU. After 1990 with the HIV-epidemic, heroin substitution with a safe opioid drug was mobilized to combat injecting practice and criminality. The traditional methadone (MDN) became challenged by buprenorphine (BPN), first in France from 1996; 10 years later the BPN alternative with naloxone (BPN-X) became a supplement in Europe. All types of different methods were evolved, each country sticking only to one. OST differ mainly in two aspects:

- 1) The treatment started by a general practitioner (GP) or a “special unit” (SU)
- 2) Buprenorphine (BPN) or methadone (MDN) as the medication of choice

The EU has for many years only warned against detoxification as an alternative to OST because of the much increased DRD [1]. I have gone further and will argue for this:

GP can independently start to prescribe BPN and tranquilizers (benzodiazepines (BZD)), while the more dangerous MDN is started by SU, like in France/Portugal. The Portuguese decriminalization of user doses also seems optimal.

Keywords

Opioid, Analgesics, Morphine, Heroin, Buprenorphine, Naloxone, Methadone, Agonist, Antagonist

Abbreviations

BPN: Buprenorphine; BPN-X: Buprenorphine+Naloxone; BDZ: Benzodiazepine; DRD: Drug related deaths; GP: General practitioner; MDN: Methadone; OST: Opioid substitution treatment; SU: Special unit

Introduction

The European Union (EU) as a source base for my research

“Never change a winning team!” is the saying. In addiction substitution

treatment the different countries may think that their method of treatment is quite optimal, which seldom is true; small changes in “the team” may revolutionize the outcome – overdoses and improved lives. I have used statistics from the European Union (EU), with its 28 member countries to grade the different OSTs. The EU has for many years arbitrarily acted as a “laboratory” with quite different OSTs. Norway contributes to this by yearly reporting, as a non-member. From this I have found it relevant to divide them into four groups for comparison: to find 1) drug superiority (among buprenorphine (BPN) and methadone (MDN)) and 2) in which instance to start opioid substitution treatment (OST) – by a general practitioner (GP) or a “Special Unit” (SU). The EU has until now concentrated more on the quality of DRD statistics than to interpret the results.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction) is the agency for drug addiction in the EU, situated in Lisbon, Portugal since 1995. Reports and some recommendations are made, based on incoming material from the members. Data on drug related deaths (DRD) are up to 30 years, as showed in Figure 1. Luckily my country Norway also reports to EU.

Drug related deaths (DRD)

A heavy heroin addict, after regular intake, of several times a day, has a high tolerance to opioids. An interruption in the intake of heroin for only half a week increases the risk of overdose. Therefore, 1) detoxification and 2) imprisonment may give deadly consequences:

1) Detoxification should be offered late in the rehabilitation process, if demanded by the patient

2) Imprisonment should be stopped for the user-only, like in Portugal after 2001 with decriminalization of user dosages [2-4]

Generally, about 80% of DRDs are related to opioids, which include heroin addiction and the treatment of it. One can deduce that it also is an indicator of the health status and thereby the rehabilitation potential in an area.

Is DRD then reliably registered to give correct trend curves to:

- Compare different countries? (EU says: “Be careful, but big differences are noticeable”)
- Follow a single country? (EU says: “This is useful as the registration differs little from year to year in each country”)

The EU has used more resources on collecting and correcting DRD statistics than to connect them to the different treatment modalities in the various countries. Response by Dagmar Hedrich (Head of sector, EU agency EMCDDA) to my findings presented at a conference was: “Although not exact, the DRDs now differ so immensely, that we may draw some conclusions on optimal OST.” Norway has had on top DRD rates, which even increased after starting a rigid OST program in 1998 (Figure 1). As GP (in Sandefjord/Norway) my interest in the treatment of heroin addicts made me try the “French method” of 1996: BPN from GPs (with

full reimbursement). I opposed the strict Norwegian rules and treated heavily heroin addicted merely as ordinary patients. The former big drug scenes vanished, paralleling DRD lowering. In my town DRDs fell to zero soon after nearly all the addicts turned from heroin to BPN. Even non-fatal overdoses disappeared.

Countries with high DRD rates may claim that one cannot trust these statistics. DRD statistics are not accurate, but the following factors suggest there may be only slight differences in developed western European countries:

- EU has for many years used considerable resources to ensure the quality of the reporting of DRD rates
- Visible, open drug scenes in a country corresponds to high DRD

To show the vast differences in DRD that developed after 1990 I have made this diagram (Figure 1) based on EU statistics for 20 (out of 28 EU countries) plus Norway, and chosen the most “western” countries. These 21 countries I divided into two:

- 1) 11 countries: GP starts OST, either by BPN (4 countries) and also with MDN (7 countries).
- 2) 10 countries: SU starts OST by BPN and MDN (which also is the method in the remaining 8 EU countries). The country with highest DRD, Estonia is the only country which offers only MDN.

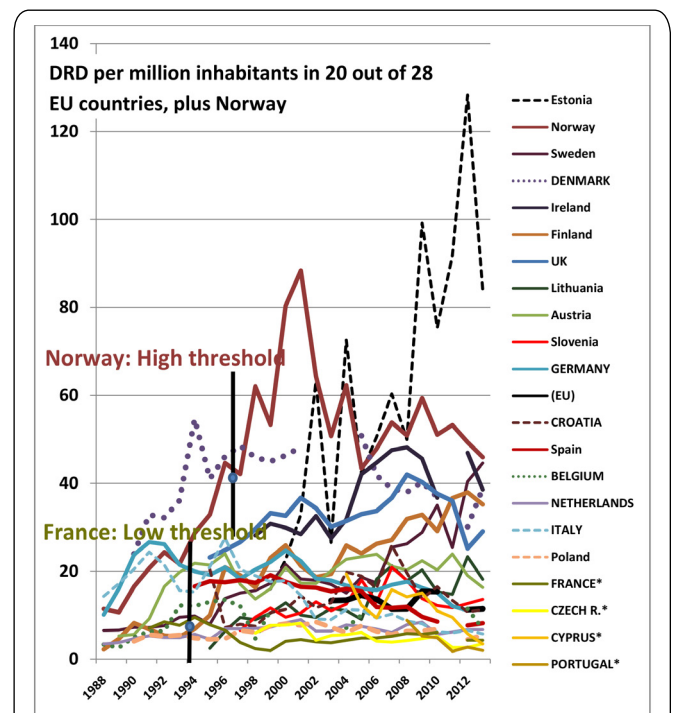


Figure 1: EU trend curves 1988–2013: Compilation of all the DRD trends (whole or fragmented), related to the actual population, from the EU annual reports, for 21 representative countries, omitting 8 mostly eastern members, with less opioid problems.

Explanation: It shows the big spread during the nineties when different OST appeared. It gives an indication that OST started by GP is superior (country name written in capital, and *: where GPs can prescribe BPN only). Countries ranked from bottom-up according to the DRD in 2013.

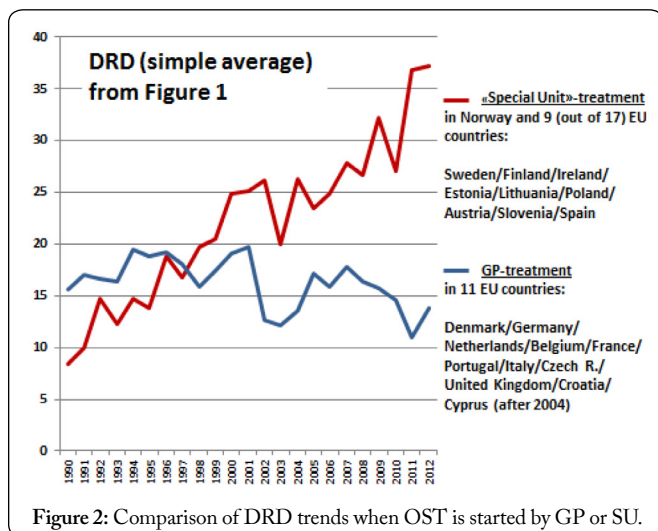
Comments: EU numbers of DRD per million inhabitants in 20 out of 28 member countries, plus Norway (marked from bottom up)(1988-2013) [5-8]. The 11 countries (written in capital) are where GP starts OST. In four out of these BPN is the only drug: Portugal, Cyprus, Czech Republic and France, which all have the lowest DRD rates. In these seven countries MDN can also be started: Belgium, Croatia, Denmark, Germany, Italy, Netherlands and United Kingdom [5]. France is marked by the year active OST was started, in 1995 with MDN; from 1996 mainly with BPN from GP. Norway is marked by the year OST was started by SU, in 1998. (In 2013 France had only 8% of the Norwegian DRD). In Estonia, with decidedly highest DRD, only MDN is given, from clinics. (See also Figure 3).

The figure 1 shows that before 1990 there were minor differences in DRD rates. In the nineties the HIV/AIDS epidemic made it crucial to reduce the practice of injecting and criminality, by substituting heroin in a safe way. It is striking that the DRD rates in all four countries where GPs can prescribe only BPN have fallen to be the very lowest.

There may be more reasons why Portugal has got the best DRD rates, when only 16 years ago having seemingly the worst rates (EU numbers are not available) as about 1% of the population were heroin addicted [2], about 3 times the average in EU countries [9]. The decriminalization of drugs for 'own use' after 2001 seems to have contributed to this – see "Discussion".

Figure 1 and 2 may point to a solution for the first of the two unsolved issues on OST:

- 1) Should the treatment be started/based by GP or SU?
- 2) Which is the drug of choice – buprenorphine (BPN) or methadone (MDN)?

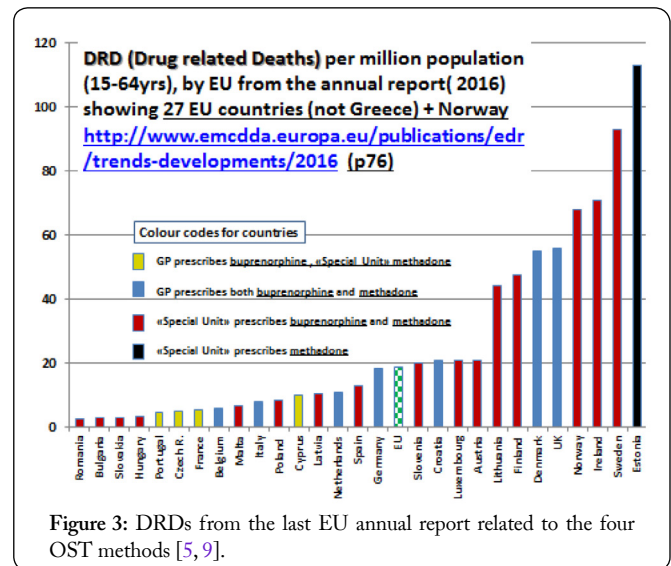


Comments: There has been a radical change in the DRD rates, with the GP-group reporting less than half the DRDs compared to the SU-group, probably after the introduction of BPN from 1996. SU OST programs, in contrast to GP OST tend to be stricter: with providers expected to stick to rules rather than give individual follow-up.

MDN or BPN?

We now have a big indication that optimal OST is by GP prescribing only BPN, reserving the more toxic MDN for SU. DRDs from the last EU annual report (June 2016) confirms

the superiority of BPN to MDN, and GP to SU (Figure 3).



Comments: In this figure four eastern countries (with less opioid [10], more alcohol problems) lie below Portugal.

How can GP treatment be so good?

People with a health problem are best taken care of by the GP, who knows you and refers when needed. The mentioned four best countries allow only BPN prescription. BPN does not need to be supervised, which is the case in France and Portugal.

I then list nine points (with further comments) for seemingly optimal OST (Figure 4): by GP starting BPN

- 1) Special training for OST is not needed
- 2) To supervise doses is not indicated
- 3) Urine tests should only be done on demand from the addict
- 4) Low dose BPN should be an alternative to high dose BPN (with or without naloxone: explained later)
- 5) Injecting practice will decrease by itself during rehabilitation so should not be treated separately
- 6) Benzodiazepine (BZD) addiction should be tapered slowly, often to a maintenance dose, as "crutches" in the rehabilitation process
- 7) Parallel psychic and somatic disease must be treated
- 8) Methadone (MDN) should be tried only when BPN fails
- 9) Alternative opioids (not heroin) may very seldom be indicated

Comments:

1) GP: A main option is that OST is provided by as many GPs as possible to avoid the mingling of these patients. GPs tend to start medication early without unnecessary delay. In the EU only Germany demands some training for GPs before OST "which may be a disincentive" [11].

2) Supervised dosing: This is a nuisance to everybody. BPN is better not to supervise because: It is a safeguarding, partly opioid antagonist, which cannot directly be combined with heroin [12]. It is the same reason why you cannot directly change from MDN to BPN, but have to shrink the dose before changing. A combination with the partly antagonist BPN causes either abstinence or less effect for several days. BPN is by itself not very toxic, about one tenth compared to methadone [12]. Without supervised dosing BPN leaks to heroin users who tend to come off, thereby enabling them to get it easily from their GP. The leakage will soon stop as the coverage is reached. BPN is unattractive as an intoxicant among non-addicts [12].

3) Urine tests: In the GP setting the addiction-related problems will be revealed without urine tests. Problematic cases are referred to SU. When positively needed, like for driving license, urine tests should be offered.

4) BPN alternatives: The traditional high-dosed BPN is efficient, but has some side-effects, although not dangerous, like headache and nausea. Adding the antagonist naloxone to BPN to avoid injecting has twice as many side-effects, but may be tried if wanted by the patient.

Another alternative, that I mean should be widely accepted for OST, is the low-dose BPN, sublingual tablets 0.2 and 0.4 mg as alternative to high-dosed sublingual tablets of 2 and 8 mg. This is an old analgesic, taken 1-2 times a day, which may at least halve the daily BPN dose, giving less side-effects and, paradoxically increases the analgesic effect.

BPN gives less Neonatal Abstinence Syndrome (NAS) than MDN [13, 14]. The low-dose BPN has been described, before 1996, to give light NAS [14].

Generally, logically it is easier to wean off from BPN by using or turning to low-dose-BPN.

5) Injections: BPN is quite often injected (methadone mixture seldom), but it will wean by itself during rehabilitation. A report from Portugal comparing two OST groups with interval of some years, showed a more than 50% reduction to 22% of injection with the opioid on attending OST [15].

6) BDZ treatment: This is better handled by GP than by SU. The use of BZD must be individualized concerning the type and dosage with a close follow-up. There are many reasons why this should be given, both health-related and criminological. This is outlined beneath.

7) Co-occurring disease: HIV and Hepatitis C are the main infections to be treated. Many psychiatric symptoms will decrease with OST, a reasonable BZD-prescription and GP follow up. More heavy problems should be referred to SU.

8) MDN treatment: The prevalence of this OST-drug should be minimized because of its higher toxicity and side-effects. It may be closely followed-up, especially when there may be leakage, when there is a lack of OST among addicts in the area.

9) Alternative opioids: Other full-agonist OST drugs are used, especially long-acting morphine (Austria, Slovenia,

Bulgaria and Switzerland (non-EU-member)) and heroin (Switzerland, Denmark and Netherlands), but these are not the very low DRD countries [9, 16].

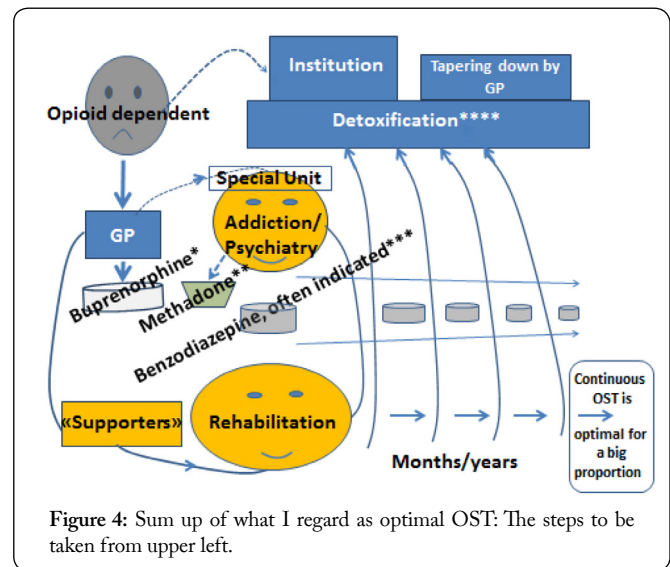


Figure 4: Sum up of what I regard as optimal OST: The steps to be taken from upper left.

Comments:

*BPN high dose once daily, in my opinion should be changed to low dose 1-2 times daily when side-effects, chronic pain and be offered in pregnancy. Strangely enough: low dosing seems to be more effective against pain. Supervised dosing is contra-productive with its relatively low toxicity and the partly antagonistic, heroin-displacing effect.

**MDN should be supervised closely, especially initially and when there is an under-prescription for OST in the area.

***BDZ is indicated when there is BDZ addiction and when anxiety supervenes, often as a side-effect of BPN. It should be tapered slowly down to zero or a low maintenance dose. There are individual preferences for the type.

****Detoxification of the opioid should not be forced upon, only offered if the addict, in a stabilized situation, really demands it. It may take months and years. With little or no real motivation, it is dangerous. A Norwegian survey showed in 2010 that the risk of overdose was increased by 14 times the first month after such a trial, because of loss of opioid tolerance [17]. A big Italian study showed even twice this: 27 [18].

More about OST-drugs and BDZs

MDN versus BPN

High-dosed BPN was introduced in France in 1996. BPN is a much safer drug than MDN. A report from France gives a good explanation for this [12]: “For 1995 to 1998, the risk of death attributed to MDN was more than 10 times higher than that attributed to BPN”. The report explains why: “BPN’s pharmacology makes it theoretically unlikely to be a substance of abuse among regular opiate users because of its mixed agonist-antagonist action, slow onset, and ability to precipitate withdrawal with agonist use.” On the issue of safety of the treatment it states: “In France, BPN maintenance treatment for problem opiate users was feasible and safe through office-based prescriptions in a relaxed regulatory environment” and “the BPN patients were more likely to inject their own prescribed BPN, whereas those MDN patients who injected

were more likely to inject heroin and cocaine” [12].

Buprenorphine-naloxone – combination (BPN-X)

The combination of BPN and the full-antagonist naloxone (BPN-X) was introduced in 2006 in Europe to inflict abstinence at injection. It has become the drug-of-choice in many countries. In *Finland* it has fully replaced BPN for eight years, with increasing and high DRDs (Figure 1 and 3). This is quite amazing as *Finland* had next to no heroin after 2004, being displaced by illegal BPN from France [19]. There may be several reasons for this bad DRD trend, like high alcohol consumption and a rigid control system. Nonetheless it is no proof for the effectiveness of BPN-X.

Quite recently the pharmacopeia shows that the BPN-X also gives twice as many (and much more serious and irreversible) side-effects than BPN alone, even organ-damage – to heart/blood/liver/kidney, resulting in more anxiousness and unrest [20]. Theoretically this should not occur, but some of it is absorbed to be metabolized by the liver, an organ that is loaded in this patient category.

Benzodiazepines (BDZ) to be substituted too

The great majority of opioid addicts experience anxiousness and unrest. There are many reasons for this [21]:

- The background (the reason for becoming drug addicted) and “outside of society”
- As a quite common side-effect of BPN
- As part of a so-called “Dual Diagnosis”, like AD/HD, depression or psychosis

The prescription of the controversial benzodiazepines (BZD) is difficult to get the full picture of globally. France and Portugal are liberal with it; Norway, Sweden, Finland and England are not. A new study from a general practice in London shows that denying BZD may increase the death rate by 4.5 times (=350%) [22].

My experience is in accordance with studies up to 36 weeks from America, Australia and Germany, that BZD from GP may reduce DRD by replacing a varied supply from the street [21].

Such intoxication hampers rehabilitation and increases criminal activity. Gilroy et al., in an Irish article refer to these studies and conclude that OST patients with more problems may use more BZD without worsening the outcome. Bought illegally the daily dose tends to be much higher and intoxicating [21]. The logic is then to prescribe enough BZD and then taper off as rehabilitation proceeds.

For a slow and gradual detoxification of opioids by the GP I am often told, and am convinced, that BZD may help to combat abstinence.

There is a big global misunderstanding that GP-prescribed BZD increase DRD, so in many places it is considered malpractice to prescribe it long-term. The Food and Drug Administration (FDA) warns against the combined prescription of opioids and BZD [23], which actually must be nuanced: The paradoxical logic seems to be that the heavier opioid addicted a person is the less is the chance of overdose

from prescribed BZD (even when injected), as the opioid respiratory depression is uninfluenced by this.

The self-treatment of anxiousness and unrest seems to be a main reason why addicts stick together in visible peer groups. Much criminality is connected to this:

- Illegal sale and use of BDZs is an offence
- The price on the street is typically 10-20 times higher than in the pharmacy
- Your preferred BDZ may not be available. For example, the common clonazepam, in high dose, is prone to reduce self-control and theft inclination.

Alcohol, a typical alternative (or supplement) to BZD is relatively cheap. It tends to be the most dangerous chemical for several reasons:

- As the most intoxicating drug the danger of injury is obvious
- It harms and damages vital organs, like liver and brain
- It interacts and increases intoxications, especially by BDZs
- The critical sense is reduced with reduced carefulness to avoid fatal outcome

Discussions

Indications for DRD as a safe parameter?

• The trend curve (Figure 1) may change markedly after the introduction of a specific, radical treatment: 1) upwards (*Norway*) after restrictive OST in 1998, 2) downwards (*France/Portugal*) with low threshold OST in 1995/2001.

The validity of DRD statistics seems to be supported by two parameters among the OST population, shown in Figure 5 and 6, percentage with:

- Earlier survival of overdose(s)
- Employment

These were two of the interesting points in a big European survey – EQUATOR (European Quality Audit of Opioid Treatment), presented in 2012 [11].

The seemingly optimal French/Portuguese model

Until 16 years ago, nearly 1% of the Portuguese population was heroin addicted, three times the EU average, with accordingly high DRD [4]. Portugal had to take radical and bold steps in 1) OST and 2) the legal system, resulting in a dramatic decrease of DRD, 80% after only a few years [2]:

1) For OST it adopted the French system from 1996 encouraging GPs to prescribe BPN, while MDN was followed up closely by SUs.

2) The pioneering “Decriminalization” means that being caught by the police with drugs for own use (for up to 10 days, with defined average amounts) is followed up as a health problem.

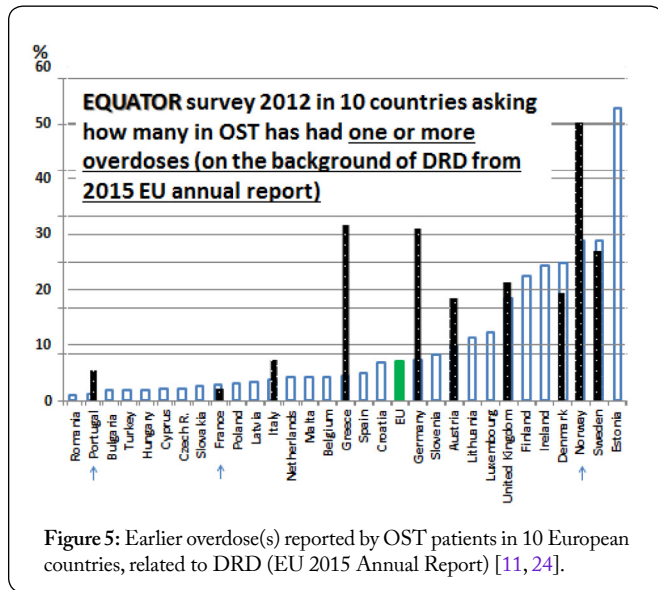


Figure 5: Earlier overdose(s) reported by OST patients in 10 European countries, related to DRD (EU 2015 Annual Report) [11, 24].

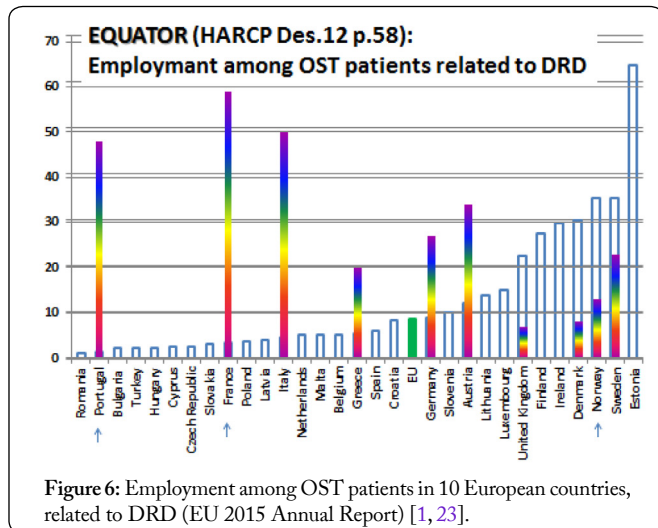


Figure 6: Employment among OST patients in 10 European countries, related to DRD (EU 2015 Annual Report) [1, 23].

Many supportive measures are also offered, like clinics and day-centers. This is well described in two articles in Washington Post [2, 3]. Most of the GP’s who deal with OST work in the Special Units (SU); like in Spain the SUs are very similar to GP treatment, making the division between GP and SU less strict. In France GPs work more independently. France had a similar decline in DRD in the nineties. From 1996 OST became really a task for GPs prescribing the more ideal BPN. Consultations is free of charge, BPN was free, but is now reimbursed by 65%. with little or no supervision of dosing. In Portugal BPN is less reimbursed, due to its economic crisis.

No other entity in medicine has had an outcome which differs so radically between the worst and the best treatment. Portugal has a DRD rate of only ¼ of EU average, which again is only ¼ of the Nordic countries Norway and Sweden; meaning that there is 16 times more chance of death from a drug related incident up north.

The DRD rate of a Norwegian city of 300.000 inhabitants (Bergen) is as high as Portugal, about 25 per year.

Until now no other country has replicated the decriminalization seen in Portugal, in spite of the immense

resources saved besides health and lives. A big threat is the increased risk of DRD after release as many then have lost their opioid tolerance [17, 25].

A wholesome view of OST

Why don’t countries learn from each other in these matters? When a system is first established it is difficult to change. The costlier and more rigid the system, the worse it is.

One denies the transfer value of DRD statistics. For example, in Norway who has a deadlocked, expensive OST, there are many away-explanations, like: “We don’t trust the DRD statistics.” “We have so many who inject compared to others, nearly all.” This is twice as many as the EU average of 40% [26]. But, it is much the other way around: Injection practice is very much a result of faulty treatment – to get the maximum out of the heroin dose. Anyway, twenty-fold difference between the best and worst country one should look for other reasons.

The “control mania” in rich countries is concentrated on those with side-abuse, a disincentive to change lifestyles, by inviting daily contact with the peer group. Those with “clean” urine tests can take the drug at home, and then sell some of the drugs.

For a global change the EU has a key role in updating their recommendations.

Conclusions

An optimal OST includes that:

- The GP is the hub in the “treatment wheel” as for all other patients.
- BPN, both in high and low dosage is much preferred to MDN.
- Supervised dosing is counter-productive, not indicated for BPN, while MDN must be followed closely.
- Benzodiazepine is reasonably prescribed to avoid dangerous side-abuse. This may actually be a major reason for the very low DRD in France and Portugal.
- Infections like HIV and Hepatitis C are treated.
- Detoxification is not only a trial, but part of a sturdy process in a stabilized patient.
- Forced detoxification may be tried in youth for a change of life.
- Decriminalization is introduced, of defined user doses, as it seems to contribute to the very low DRD in Portugal. OST also greatly reduces criminality by itself, as in this Norwegian study [27].

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