Should Methadone and/or Buprenorphine be included in the WHO Model List of Essential Medicines?
Reviewing evidence from Iranian experience.

MT Yasamy, MD *

“Essential drugs are those that satisfy the health care needs of the majority of the population; they should therefore be available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford. This concept is intended to be flexible and adaptable to many different situations; exactly which drugs are regarded as essential remains a national responsibility.”

“An evaluation process is therefore necessary, based on a comparison between various drug products and on cost/benefit considerations. The advantage of a new treatment over the existing one is then compared to its extra cost”


The recent Submission for the above mentioned medications to be added to the WHO essential Mode List covers a comprehensive review of relevant evidence. We are going to share the available evidence, though limited, from a lower middle income country with public health problems related to opioid substances. Our discussion will address the above mentioned statements defining essential medicines.

A. Do methadone and/or buprenorphine satisfy health care needs of the majority of the population?

A1. Is opioid involvement a major public health problem?

Opium smoking has been common in Iran since centuries. But the magnitude of social, economic, familial and health related outcomes of opioid use has been changing over time. According to more recent national surveys prevalence of drug dependence exceeds 2%. There are more than 1.200.000 opioid dependant persons, adding to this the number of abusers yields about 2.500.000 problem users. The number of persons suffering from opioid involvement problems including intravenous drug users (IDUs) has been increasing (Razzaghi et al, 1999; Razzaghi et al, 2002; Yasamy et al, 2002; Rahimi Movaghar, 2003). Half of the IDUs have started injecting after 1993 (Razzaghi et al, 1999).

The amount of illicit drugs seized in the country is considerable too. In 1990, 1995 and 2000 increasing amounts of 27.6, 150 and 250 tons of illicit drugs were seized. Authorities believe that the seizures usually comprise 10-20% of the total amount

* Director, department of mental health, Ministry of Health, I.R. Iran
of drug entering the country (Mokri 2002, Drug Control Headquarters, 2001). Though
the main part of the illicit drugs seized has been bound to transit from Iran, an
unknown proportion precipitates in the country for local users.

Opium and heroin are the primary drugs of abuse in the nation. The proportion of
heroin to opium users is increasing. Most heroin users begin with opium
consumption and for controversial reasons convert to heroin, and heroin users
more readily convert to IV drug use (Mokri, 2002).

There are between 100,000 to 130,000 IDUs (Razzaghi et al 2002; Yasamy, 2002). The
greatest majority injects opium and heroin. According to Yasamy et al 2002, buprenorphine
was much more frequently abused compared to methadone and most buprenorphine users were injecting it. According to Razzaghi et al 2002 who
focused on IDUs, common injected drugs include heroin, opium, buprenorphine,
methadone and, diazepam. Needle and equipment sharing is between 30% to 100% in different districts. A half of IDUs have a history of promiscuity, more
commonly with multiple sex workers. Sex workers themselves are commonly drug
users, half of them IDUs. Protected sex is not a common habit. Overdose is a
common complication. Two third of IDUs have a history of imprisonment. Half of
the prisoners who had used drugs while in jail had shared needles.

A third of IDUs are estimated to be Hepatitis C positive. Overall, 63% of HIV
positive and 34.7% of AIDS patients have been IDUs (Razzaghi et al 2002).

Based on the above findings, Opioid involvement is a major public health problem
in Iran.

A2. Do methadone and/or buprenorphine satisfy health care
needs related to opioid involvement?

A2.1 Methadone

Long before the emergence of AIDS pandemic, when heroin dependence was
quite rare and IV injection unknown in Iran; "addiction" was perceived as harmful to
health and received treatment. Though the abstinence model was dominant;
methadone was widely used in parallel with “opium tablets” for opioid detoxification
within inpatient and outpatient facilities (Siassi 1976, Moharreri 1976). Based on an
observational study, from a total of 533 patients in one setting, 347 did not enter
the treatment or did not continue it beyond the first few sessions. Only 35% were
able to finish the detoxification course. Diversion of medications was a problem.
Side effects were less frequent in those on methadone (Moharreri, 1976).
Methadone maintenance was about to expand but the new legislation, which
declared addiction as crime suspended all agonist treatments. It took more than
two decades that the rapidly increasing IV drug use in the nation and the emerging
HIV/AIDS problems called for a radical revision of policies.

Clinical trials with methadone

In September 2002 a UNODC sponsored clinical trial on the efficacy of MMT was
initiated. According to the submitted report (Mokri, 2004):

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- MMT decreases illicit opioid abuse, criminal and violent behavior and helps patients spend a reasonable sum of money formerly spent on drug consumption.
- MMT with doses below 20 mg/day is highly unpractical and useless and associated with high dropout, patient complaint and illicit drug use.
- Increasing the methadone dose from 40 mg/day to 75 mg/day was accompanied by an increase in treatment retention from 53% to 89% at the end of 3 months. The above-mentioned study was limited to the hospital settings and had a fixed randomly selected dose.

A second extended clinical trial (Razzaghi et al 2004) was designed in which open label feasibility study of MMT in the hospital and community settings was addressed. Inclusion criteria were relaxed and patients could choose to enter MMT or usual services offered at the clinic.

**Main outcomes of trials with methadone**

- MMT has a high retention rate exceeding 2/3 for 3 months.
- MMT is associated with large reductions in criminal and HIV related high-risk behavior.
- Optimum dose for MMT is above 75 mg/day. Doses below 30mg/day are associated with high dropouts.
- Patients staying more than 3 months in treatment are mostly reluctant to exit at least in the coming 2 years.
- Improvement seems to continue even after 2 years of treatment.
- Not all clients agree with the terms of MMT. Three out of 4 and mostly opium users find the schedule too demanding or unnecessarily long.

There have been many other centers working on MMT but they have not published their results.

**A2.2 Buprenorphine**

According to a series of articles published by Dr Ahmadi and colleagues from Shiraz, Buprenorphine has been used successfully as maintenance therapy for opium and heroin dependency ,but completion rates were highly dose dependant. They suggest that an adequate dose should be used, and that 8 mg per day has been recommended as the best dose (Ahmadi , 2002 (a, b); Ahmadi and Bahrami, 2002; Ahmadi et al, 2004). Compared with methadone, they support the superiority of 30 mg of methadone compared to 1 mg dose of buprenorphine for Iranian heroin-dependent patients to increase their retention in treatment ( Ahmadi, 2003).

Another issue about buprenorphine in Iran has been the fact that initial advent of this potentially useful medication did not take place by health workers .The injection form was widely distributed by drug dealers and the black market, buprenorphine was identified as a drug of injection by IDUs (Yasamy, 2002; Ahmadi et al, 2003) and in recent years it has been observed that opiate users increasingly use the

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injectable form of buprenorphine (WHO, EMRO, 2004). According to Ahmadi et al, 2003 methadone has been shown to be superior to buprenorphine and both have been shown to be superior to naltrexone as maintenance treatment for IV buprenorphine dependents.

*Based on the above findings, from a technical (effectiveness) point of view both medications satisfy health care needs related to opioid involvement. But methadone is occupying a higher position because it has been used much less frequently as a drug of injection by IDUs in Iran.*

**B. Are these two medications available at all times in adequate amounts and in the appropriate dosage forms, and at a price that individuals and the community can afford?**

According to the main clinical trial undertaken in Iran, MMT can be offered at rates as low as 15 $/month per client. Clients save more than 100 $ a month after entering MMT (Razzaghi et al, 2004). *The price of MMT is affordable by most Iranians so far as they receive it from the public sector.* Based on the information collected by the author from different sources, one single 5 mg tablet in Iran costs about $0.01 in the public sector but it costs about 1 dollar in the black-market. It is conceivable that such a difference in prices makes diversion prevention very difficult, but it seems that the more the drug users are covered by the health sector the more the demand for black-market will decline.

Some other trials and cost studies on buprenorphine are under way in Tehran but the results are not available at this point. Buprenorphine 8mg is not still available in Iranian black-market but 0.2 mg tablets cost about half a dollar, and drug users use it mainly for detoxification. On the other hand, because the injection form costs only about one dollar in the black-market and the absorption is more predictable, it is being commonly used as a drug of abuse. Since the original European and American market prices for 8mg buprenorphine tablets are quite high for Iranians (about 4 - 8 dollars?) and at least 8mg/d is needed for maintenance programs, it is conceivable that even if they enter the country the *prices will not be affordable for most individuals and the community.*

**Concluding remarks:**

According to expert committee recommendations:

*“Based on a comparison between various drug products and on cost/benefit considerations, the advantage of a new treatment over the existing one is then compared to its extra cost”*

Based on information available at the national level at this point, methadone but not buprenorphine can be recommended to be included into the essential medicines model list, preferably the complementary list. The fact that Iran is producing generic methadone, that there is more than 3 decades of national experience on methadone, that buprenorphine has been more frequently injected
by IDUs in Iran and that it arrives with a very high price here has clearly influenced this suggestion.

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