

## **DISCUSSION**

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Heroin dependents are those who continue to use heroin in the face of difficulties they know or believe to be caused by its use such as health, legal and inter-personal difficulties. They typically use heroin daily, develop tolerance to its effects, and experience withdrawal symptoms on abrupt cessation of use. About one quarter of people who have ever used heroin developed dependence (Anthony and Helzer, 1995).

Dependence does not end when the drug is removed from the body (detoxification) or when the acute post-drug taking illness dissipates (withdrawal). Rather, the underlying addictive disorder persists, and this persistence produces a tendency to relapse to active drug taking (O'Brien and McLeVan, 1996).

Methadone maintenance treatment (MMT) is the most extensively researched form of maintenance treatment for opioid dependence. The effectiveness of treatment for opioid dependence would ideally be assessed through randomized controlled trials (RCTs). Only five such trials have ever taken place in the 35 years since MMT was introduced. All five trials involved small number of patients who were rarely followed for longer than one year. The effectiveness of MMT in observational studies of community treatment programmes has not been as impressive as that in the RCTs, indicating that methadone treatment in routine use is not a panacea for opioid dependence. About half of those who enter treatment

left within 12 months, and some of those continued to use heroin and other illicit drugs though much less frequently than before they entered treatment (Hall et al., 1998).

Maintenance with pure opioid antagonists such as naltrexone has been shown to be effective in opioid dependent people for whom failure to comply with treatment has major personal consequences (e.g. opioid dependent health professionals) but pure opioid antagonists have not proven popular with the wider population of opioid dependent people, in whom low rates of compliance have been a major difficulty. Naltrexone has almost no agonist effects and will not satisfy craving or relieve protracted withdrawal symptoms. For these reasons, naltrexone treatment does not appeal to the average heroin addict especially those with less motivation to remain opioid free (O'Brien, 1996).

The study, we proposed, was the first project launched in the Department of Pharmacology and Therapeutics, University of Karachi. The objective for this project was to search for non-opiate treatment of opioid dependence for long term management; a treatment which would be more safe, less hazardous and more acceptable to opioid addicts.

Prior to this few studies were conducted at Basic Medical Sciences Institute, J.P.M.C., Karachi, in which the role of calcium channel blockers was observed in the treatment of opioid dependence syndrome. These studies were carried out by Baloch (1991), Mahesar (1994), Salat (1998), and

Ansari (1999) in which effect of calcium channel blocker in treatment of opioid dependence was evaluated in animal and patients.

Baloch (1991) and Mahesar (1994) observed the effect of verapamil and felodipine in morphine dependent animals subjected to naloxone in vivo and vitro. They observed that calcium channel blockers were effective in reducing the abstinence in vivo and in vitro effects. These observations led to pilot project on morphine addict patients.

First clinical study was conducted by Salat in 1998, who compared the effects of calcium channel blocker, verapamil with thioridazine and amitriptyline, contemporary treatment prevalent in Karachi in the management of acute opioid abstinence syndrome.

He observed that verapamil showed a highly significant improvement in signs and symptoms of abstinence. The patients, who were admitted during the study with previous history of opioid abstinence without treatment, expressed that they did not experience these withdrawal effects. He concluded that verapamil therapy is safe, effective, and more pronounced in treating the acute opioid withdrawal syndrome than amitriptyline and thioridazine.

Second clinical study was done by Ansari (1999) in which the effects of verapamil and clonidine compared with thioridazine and chlorpromazine in opioid abstinence syndrome were observed. He observed that the effects of verapamil and clonidine to decrease the signs

and symptoms of acute withdrawal from opioids were highly significant when compared with chlorpromazine and thioridazine.

Hence, in the light of previous clinical studies, this single blind study was proposed to observe the effects of *Nigella Sativa* in long term management of opioid dependence. Each patient received treatment initially for 12 days during his stay in hospital. Then each patient was advised for weekly follow up as out-patient and the same treatment was continued till eight weeks, then the dose of drug was gradually tapered off during next two weeks period after that patient was followed up further for two weeks without giving any drug.

A placebo for the drug was given on day-1 and 2 of admission, only to observe and confirm the opiate withdrawal syndrome on first three days of admission. *Nigella Sativa* was administered in dose of 250 mg and 500 mg three times daily, in the two groups. Each group comprised of 25 patients. *Nigella Sativa* produced a decrease in opiate withdrawal signs and symptoms.

*Nigella Sativa* 250 mg reduced the subjective symptoms from pretreatment day-3 scoring rate of  $55.08 \pm 12.65$  to  $29.4 \pm 5.02$  at day-12. Similarly, objective signs were also reduced from pretreatment day-3 scoring rate of  $19.76 \pm 4.58$  to  $12.12 \pm 2.60$  at day-12.

Regarding the physiological parameters decrease was observed in pulse rate, systolic blood pressure, diastolic blood pressure, and

temperature, but all were within normal physiological ranges. Respiratory rate and pupil diameter also decreased. Both body weight and caloric intake increased.

Similarly, *Nigella Sativa* 500 mg was given to 25 patients three times daily throughout the treatment period after abrupt discontinuation of opioid administration. It also produced rapid decrease in opiate withdrawal signs and symptoms. The subjective symptoms were reduced from pretreatment day-3 scoring rate of  $63.2 \pm 13.57$  to  $14.56 \pm 8.13$  at day-12. Similarly objective signs were also reduced from pretreatment day-3 scoring rate of  $25.52 \pm 3.08$  to  $7.72 \pm 2.35$  at day-10.

Maintenance with opioid agonists methadone or L- $\alpha$ -methadol (LAAM), antagonist (naltrexone) or partial agonist (bupremorphine) is the usual practice in the long term management of opioid dependence, but all these drugs have their own disadvantages. It has been proved in many invitro studies that calcium channels/blockers, modulate the opioid receptors or release of endogenous opiopeptins in one or other way (Hernandez et al., 1993; Martinez et al., 1993; Smart and Lambert, 1996; Sher et al., 1996; Spampinato et al., 1994; Simmons, 1995; Fields and Sarne, 1997; Schwartz and Katki, 1990; Vonvoigtlander et al., 1987; Bongiani et al., 1986).

We found only one *in vivo* study (Shulman et al., 1998), in which the calcium channel blockers, verapamil or nifedepine were used in only

three patients for 2-8 weeks after detoxification. It was observed that calcium channel blockers prevent the development of significant craving and prevent the relapse. There was an increased sense of well being, manifested as less anxiety, clear thoughts, more satisfying sleep (often without sedatives), and a greater desire and capacity to participate in social and sporting activities. None of the patients suffered severe calcium channel blockers evoked adverse effects and none required cessation of calcium channel blocking agent.

There were 20 symptoms in the opiate withdrawal questionnaire used in previous studies with minimum score of zero to maximum 80. Grading of intensity of symptoms were from 0-4 with increasing severity. While the state used in our study had 38 subjective symptoms with a maximum score of 152. The additional symptoms were added for the more comprehensive assessment of the state of acute withdrawal as well as for assessing the state of protracted withdrawal after the acute abstinence. The additional symptoms were such as decrease in appetite, alertness, cheerfulness, calmness, patience, relaxation, and clear thinking, disorientation, carefreeness, drug craving, dysphoric mood, feelings of anxiety, increased sensitivity to pain, low psychomotor speed, pounding heart, sadness and shooting up.

Similarly, there were only six signs in opiate withdrawal questionnaire in previous two studies with minimum score of zero to maximum 24.

Grading of intensity of signs were from 0-4 with increasing severity. While the scale used in our study had 18 objective signs with a maximum score of 72. The additional signs were added for the more comprehensive assessment of the state of acute withdrawal as well as for assessing the state of protracted withdrawal after the acute abstinence. The additional signs were such as air, hunger, anorexia, insomnia, mydriasis, and tremor.

As it was proved in an in vitro study that *Nigella Sativa* is having calcium channel blocking effect (Gilani et al., 2001), along with analgesic, spasmolytic, anti-microbial, and anti-diarrhoeal etc., effects so this drug was used in this study. It is concluded that this drug is effective in long term management of opioid dependence.

It not merely cures the opioid dependence but also cures the infections and weakness from which majority of addicts suffer. It is suggested that further long-term follow up studies are needed to evaluate the benefit of this drug in maintaining the patients opioid free. In addition, various biochemical and physiological evidences are required to further strengthen the effectiveness of this non-opiate drug in long-term management of opioid dependence.