A NEW AND NOVEL TREATMENT OF OPIOID DEPENDENCE: *NIGELLA SATIVA* 500 mg.

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Background: Opioid dependence is one of the major social and psychiatric problem of society. Unfortunately there is no non opiate treatment available. For centuries man has used plants for their healing proprieties. These plants play a fundamental part in all treatment modalities, both ancient and modern. **Methods:** This study was conducted to find non opiate treatment for opiate withdrawal. Total 35 known addicts of opiates were included in the study. This study was based on DSM IV criteria for opioid dependence. **Result:** This study demonstrates that non opioid treatment for opioid addiction decreases the withdrawal effects significantly. It further demonstrates that there are no changes in physiological parameters of subjects during treatment (BP, Pulse rate etc.). There is increased appetite but no significant weight gain in the subjects. **Conclusion:** Non opioid drug *Nigella sativa* is effective in long term treatment of opioid dependence. It not merely cures the opioid dependence but also cures the infections and weakness from which majority of addicts suffer.

Keywords: Niggella sativa; Opioid addiction.

INTRODUCTION

Drug dependence is a condition in which an individual feels compelled to repeatedly administer a psychoactive drug. Repeated drug use appears to be a learned behaviour that is reinforced both by the pleasurable effects of the drug and by the negative effects of drug abstinence (withdrawal).[1] Both psychologic and physical dependence appears to result from neuronal adaptation to the presence of the drug in different areas of the brain.

The craving for alcohol, barbiturates, caffeine, cocaine, opioids and phencyclidine is remarkably similar, despite the varied behavioural and physiologic effects that these drugs produce. The similarity supports the hypothesis that psychologic dependence is mediated by a common neuronal pathway that leads to behavioural reinforcement of drug use.[2] Physical dependence appears to result from the adaptation of specific areas of the brain to the continued presence of a drug. Physical dependence is associated with drug tolerance and with the development of a drug-specific withdrawal syndrome.[3] Addiction is usually associated with a high level of drug dependence.[4] The most commonly abused opioid drug and one of the most widely used street drugs is heroin. This drug is prepared from morphine after its extraction from raw opium. It is highly lipid-soluble and rapidly enters the CNS following injection, Heroin may produce an intense euphoric sensation called a RUSH. Long term heroin users develop considerable drug tolerance and physical dependence, and they undergo a wide variety of withdrawal symptoms if they abruptly discontinue their use of the drug.[5] Other opioids produce effects similar to those of heroin, but usually to a lesser degree.[6] An orally administered drug such as methadone is used to prevent the craving for heroin as well as the opioid withdrawal reaction without causing significant reinforcement or exacerbating drug dependence.[7] Opioids produce their effects by acting at mu (mu1, mu2, mu3, mu4 and mu5), kappa (kappa1 and kappa2), delta, sigma and epsilon, receptors. Opioids inhibit synaptic activity, partly through direct activation of opioid receptors and partly through release of the endogenous opiopeptins (endorphins, dynorphins and enkephalins). All these major opioid receptors are coupled to their effectors by proteins and activate phospholipase C or inhibit adenylcyclase. Activation of these receptors either opens K channels to cause membrane hyperpolarization or closes voltage gated Ca channels to inhibit neurotransmitter release.[8]

Management of drug abuse

The clinical problems caused by the use of psychoactive drugs vary markedly among different classes of drugs and patterns of drug use. A diagnosis of drug dependence in a particular person is primarily based on the history, Psychologic assessment, physical examination and laboratory findings. After proper management of the case is very essential to bring the patient back to life, the management usually includes:

Psychotherapy, Medication, Occupational therapy, behaviour therapy and Rehabilitation.

Nigella Sativa

Nigella Sativa Linn belongs to family Ranulaceae. The herb is widely known in different parts of the world and its seeds are used as condiment. In subcontinent it is known as '*kalonji*' and its Arabic name is '*Habatul Sauda*'.[9] In the west it is known as "Black Cumin". There is a Hadith of Hazrat Muhammad (PBUH) that, '*black seed is treatment of every disease but death*'.

It has been proved scientifically *in vitro* and *in vivo* studies that volatile oil of *Nigella Sativa* seeds

inhibited the spontaneous movements of rat and guinea pig uterine smooth muscle and also the contractions induced by oxytocin stimulation.[10] It has also been found as contraceptive,[11] and anti-inflammatory.[12] The volatile oil possess the potential of being a potent centrally acting anti-hypertensive agent. It has also been found potential centrally acting respiratory stimulant.[13] Nigellone is the carboxyl polymer of thymoquinone, isolated from *Nigella sativa* Linn seeds. Nigellone in relatively low concentrations is very effective in inhibiting histamine release induced by the secretagogues: antigen in sensitized cells.[14] The active principle of *Nigella sativa* seeds containing certain fatty acids was studied for anti-tumour activities against Ehrlich ascites carcinoma (EAC), Daltons lymphoma ascites (DLA), and sarcoma-180 (S-180) cells. In vivo EAC (Ehrlich ascites carcinoma) development was completely inhibited by the active principle.[15,16] *Nigella sativa* seeds causes concentration dependent inhibition of gram-positive bacteria, gram-negative bacteria and a pathogenic yeast candida albicans.[17]Anticestodal effect of *Nigella sativa* seeds was studied in children infected with worms. It is conceivable that the plant contains active principle effective against nematodes and cestodes. The crude drug did not produce any adverse side effects in the doses tested.[18] Plant mixture extract comprising of *Nigella sativa*, Mynh, Gum olibanum, Gum asafoetida, and aloe to have a blood glucose lowering effect.[19] *Nigella sativa* is used in Arab folk medicine as a diuretic and hypotensive plant.[20] it also works as hepato-protective.[21] The *Nigella sativa* oil and thymoquinone produce antinociceptive effects through indirect activation of the supraspinal mu1 and kappa-opioid receptor subtypes.[22] Phytochemical studies on seeds revealed the presence of volatile oil (1.5%), fixed oil (37.5%), nigellin, melanthin and thymoquinone. The volatile oil consists mainly of carvone (45–60%), carvene, cymene and thymoquinone.[23] Nigellidine, nigellimine, and nigellicine are the alkaloids isolated from the black seeds, these are devoid of pharmacological effects.[24] The crude extract of *Nigella sativa* seeds has been studied in vitro for its possible spasmolytic and bronchodilator activities to rationalize these medicinal uses. Ns.Cr causes a dose-dependent relaxation of spontaneous contraction. Ns.Cr also inhibited potassium-induced contractions in a similar dose range, suggestive of calcium channel blockade. this activity is concentrated in the organic fraction.[25] The seeds of *Nigella sativa* contain a yellowish white volatile oil (0.5–1.6%) fixed oil (35.6–41.6%), proteins, aminoacids, e.g., albumin, globulin and valine reducing sugars, mucilage, alkaloids, organic acids, tannins, resins, toxic glucoside, metarbin, bitter principles, glycosidal saponins, melanthin resembling helleborin, melanthigenin (1%), ash, moisture, and Arabic acid. The seeds have also been found to contain fats, crude fibre, minerals, e.g., Fe, Cu, Zn, P, Ca and vitamins like thiamine, niacin, pyridoxine and folic acid, they also possess nutritional value.[26] *Nigella sativa* seeds yield esters of fatty acids, e.g., oleic acid, linoliec acid, and dehydrostearric acid, higher terpenoids, aliphatic alcohols, and α-β unsaturated hydroxyl ketones.[27] Free sterols, steryl esters, steryl glucosides and acylated steryl glucosides were isolated from the seed oil.[28] A novel alkaloid, nigellicine, an isoquinoline alkaloid, nigellimine, and an indazole alkaloid, nigellidine, were also isolated from the seeds of *Nigella sativa*.[24] The active constituents of the seeds include the volatile oil consisting of carone, and unsaturated ketone, terpene or d-limonene also called carnone and cymene.[27] The crystalline active principle, nigellone, is the only constituent of the carboxyl fraction of the oil. Pharmacologically active constituents of the volatile oil are thymoquinone, dithymoquinone, thymohydroquinone, and thymol.[29]

Since the ancient times, the plant is being used for several ailments, as in infectious diseases or metabolic disorders. It has also been used traditionally as spice, carminative, condiment, aromatic, stimulant, diuretic, stomachic, liver tonic and digestive. It has also been found useful in loss of appetite, vomiting, and puerperal diseases. It is also used commercially as emmenagogue and galactagogue and stimulant of uterine contractions. It is also used as natural remedy for amenorrhoea and dysmenorrhoea. It has remained in use for hepatic and digestive disorders as well as in chronic headache and migraine. Its traditional uses also include obesity, dyspnoea, eczema, pityriasis, mercury poisoning, sores and leprosy.[30] It is also given in leucoderma, alopecia, eczema, freckles, and pimples.[31]

This study was conducted to find a non opiate drug, which should not be having any euphoric or withdrawal effects and that can treat the opioid dependence syndrome effectively. Reducing the extent of drug dependence is one of the major goals of medicine.[32] As *Nigella sativa* has been found to have calcium channel blocking ability, inhibiting action potential in neuronal as well as peripheral tissues and calcium channel blockers have been proved to be effective in opioid withdrawal syndrome so purpose of present study was to evaluate the effects of *Nigella sativa* in opioid dependence.

MATERIALS AND METHODS

This study was carried out at the Drug Rehabilitation Centre, RHC Murad Memon Goth, Malir, Karachi and in the Department of Pharmacology, University of Karachi. A total of 50 male opiate addicts who were seeking treatment for opioid dependence were consecutively admitted between September 2001 to September 2003. All were admitted for 12 days to treat acute opiate withdrawal syndrome and then treated for opioid dependence as outpatients for 12 weeks.

Selection of Patients

All patients in the study were selected according to the following criteria:

Inclusion Criteria

1. Males between 21 and 45 years of age seeking treatment for opioid dependence for duration of three months.
2. Following routine clinical criteria indicating opioid addiction were observed:
   a. Self reported duration of opioid dependence of at least four months.
   b. An average of two or more episodes of opioid use per day.
   c. Physical evidence of recent intravenous drug use (tracks).
   d. Urine toxicology positive for opiates at entry to the study.
   e. A rating of two or greater on a self reported level of withdrawal scale 12 hours after the last opioid use.
3. Ability and willingness to give informed consent.

Exclusion Criteria

1. Psychiatric illness, e.g., anxiety, neurosis, phobia, obsessive compulsive neurosis, and hysteria.
2. Self reported current dependence on alcohol or other major drug of abuse like sedatives, hypnotics (including benzodia-zepines), cocaine, or amphetamines.
3. Acute liver or cardiovascular diseases.
4. Current enrolment in an opiate treatment programme.
5. Any debilitating disease.[40]

Materials

1. Dried black seeds of *Nigella sativa* (*Kalonji*) were purchased from Majeed Brothers, Lajpat Road, Hyderabad, and were cleaned off from adulterant materials and were ground with an electric grinder into coarse powder.
2. Empty capsules manufactured locally were purchased from open market.
3. The frontline opiates test strips obtained from Boehringer Mannheim Pakistan (Pvt) Ltd., Ch-B/Lot No. 28739531 and expiry in February 2004.

Treatment Schedule

The selected patients with opioid dependence were kept on 500 mg *Nigella sativa* orally TID.

The patients received single blind placebo capsule (orally) containing ferrous sulphate powder of same colour, size and shape for the drug, during day-1 and day-2 of admission. They were observed and rated for the presence and absence of opioid withdrawal signs and symptoms experienced during the previous 24 hours by an observer. Thereafter each treatment, group received single blind capsule, containing 500 mg *Nigella sativa* on day-3 of admission (treatment day-1). After the initial administration, patients with a positive response to the drug in terms of opiate withdrawal signs and symptoms and without producing side effects were given the drug up to day-12 of admission (treatment day-10). Diazepam 5 mg was prescribed for some patients having anxiety. The ratings covered the withdrawal signs and symptoms during the previous 24 hours. All the patients received their respective treatment up to day-12 of admission during their stay in hospital. After that patients were discharged on the same treatment and advised to attend OPD weekly up to twelve weeks.

The study was carried out according to the following protocol:

1. Permission was obtained from the Incharge Medical Officer of the Rehabilitation Centre, R.H.C., Memon Goth, Karachi.
2. All the patients met inclusion and exclusion criteria for admission to the study.
3. Consents were obtained from all patients before they were enrolled in the study.
4. On entry in the study, the patients received complete physical examinations including electrocardiograms and laboratory screening tests (complete blood cell count, serum chemistry for hepatic functions and urine analysis) to exclude any pathology.
5. All the patients were admitted to the hospital for 10 days for the treatment of acute opiate withdrawal syndrome.
6. The inpatient records of each group were recorded on a proforma .
7. The severity of opioid abstinence syndrome of each patient during admission and during follow up was recorded on a proforma especially designed for this study.
8. All the patients were physically dependent on heroin, with a model dose range 'between ¼ and ½ grams' (street doses) per day.
9. To ensure that the patients during the protocol did not covertly ingest other drugs. They were confined to a locked inpatient unit, and visitors were restricted. However, patients could discontinue their participation in the protocol and leave the unit at any time on request without prejudice to their future treatment.
10. The patients received single blind placebo capsule for each drug during day-1 and 2 of admission and they were observed and rated for the presence or absence of opioid withdrawal signs and symptoms experienced during the previous 24 hours.
11. On day-3 of admission single blind treatment with *Nigella sativa* was assigned in a random manner.
12. After the initial *Nigella sativa* administration, patients with a positive response to drug in terms of opiate withdrawal signs and symptoms and without producing side effects were given drug up to day-12 of admission.

13. Urine samples were collected, on day-1 and 12 of admission and tested immediately for opioids by test strips.
14. Patients were discharged after 15 days of admission and then assessed weekly up to twelve weeks.
15. Each patient received the treatment for eight weeks and then the doses of drug were gradually tapered off during next two weeks that is weeks-9 and 10.
16. During last two weeks, that is, weeks-11 and 12, patients were assessed without given any drug.
17. Urine samples were tested for opioids on weeks-4, 8 and 12 during the follow up period.
18. This study was carried out on 50 patients. Total period of study was two years.

Data was statistically evaluated. The selected patients were enrolled, data and progress of the patients were recorded which included the parameters for abstinence as well as protracted withdrawal for opiate dependence.

Subject-Reported Measures

It was in the form of modified subjective opiate withdrawal scale (MSOWS), which contained 38 opiate withdrawal symptoms. Subjects indicated the degree to which they had experienced each symptom during the past 24 hours on a five point scale in which 0=not at all, 1=a little, 2=moderately, 3=quite a bit, and 4=extremely (maximum possible total score was 152). The ratings for individual item were summed for a total score each scale.

Observer Rated Measures

It was in the form of objective opiate withdrawal scale (OOWS) containing 18 observable physical signs. An independent observer observed and rated the presence and intensity of signs on a five point grade scale in which 0=not at all, 1=a little, 2=moderately, 3=quite a bit, and 4=extremely.[41]

Physiological Parameters

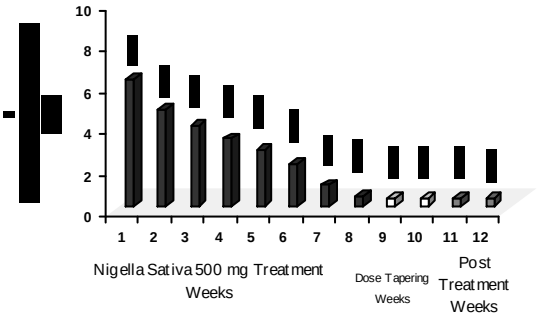
It includes the pulse rate, systolic blood pressure, diastolic blood pressure, temperature, respiratory rate, body weight, and caloric intake.[42]

Urine Analysis Measures

Urine samples were collected on days-1 and 12 of admission and then on weeks-4, 8 and 12. All samples were collected under staff observation to deter bogus urine samples and tested immediately for opioids by using one-step dip and read chromatographic test strips (Frontline opiates test strips).

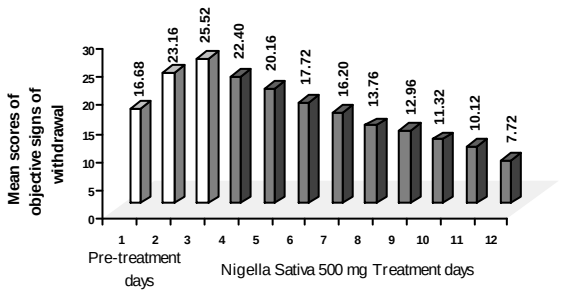
RESULTS

Total 35 patients were enrolled in the study; out of these, 10, patients were dropped during first and second weeks of treatment. All patients were men ranging in age from 21–44 years (x=33.152±0.421). They all expressed interest in discontinuing the use of opioid and gave written consents to join the study that required an abrupt withdrawal from opioids after admission to hospital. They had a mean of 4.957±0.553 years history of opioid consumption (range 1–15 years). All had subjective symptoms and objective signs of opiate withdrawal and urine specimens showing positive results when tested with frontline opiates dipstick-subjects of *Nigella sativa* 500mg treatment showed minor adverse effects. Our final analysis applies to 25 patients who completed the protocol: *Nigella sativa* 500 mg orally TID. Some patients received Diazepam 5 mg for night time sedation. The results show a cumulative score of opiate withdrawal signs and symptoms on day-1 to day-12 of admission and then on week-1 to week-12 as outpatient. The degree of withdrawal signs and symptoms were assessed according to the scoring system described in methodology.



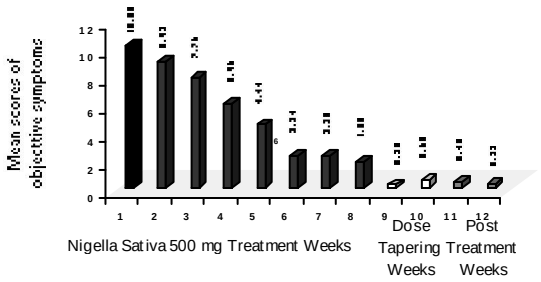
Effects of *Nigella sativa* 500 mg treatment on the Mean±SEM scores of 38 symptoms of withdrawal of the 12 days sample in 25 opioid addicts at days after the 3rd inpatient day of withdrawal. Students'*t*-test comparing change in symptoms day-12 indicated trend decrease in symptoms to be reported on day-12 of admission.

Figure-1: Effects of *Nigella sativa* 500 mg Treatment on Subjective Symptoms of Withdrawal from Opioids during 12 days stay in Hospital



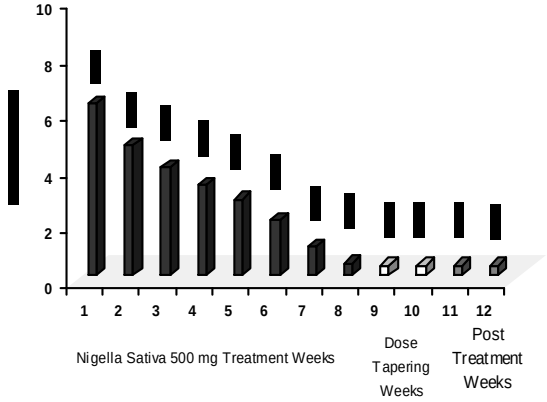
Effects of *Nigella Sativa* 500 mg treatment on the mean±SEM scores of 18 signs of withdrawal of the 12 days sample in 25 opioid addicts at days after the 3rd inpatient day of withdrawal. Students' t-test comparing change in signs from pre-treatment inpatient day-3 to treatment day-10 indicated trend decrease in signs to be reported on day-12 of admission.

Figure-2: Effects of *Nigella Sativa* 500 mg Treatment on Objective Signs of Withdrawal from Opioids during 12 days stay in Hospital



Effects of *Nigella Sativa* 500 mg treatment on the mean±SEM scores of subjective symptoms of protracted abstinence in 25 opioid addicts after every week during 12 weeks of follow up.

Figure-3: Effects of *Nigella sativa* 500 mg Treatment on Subjective Symptoms of Protracted Abstinence in patients with Opioid Dependence during 12 weeks of Follow up



Effects of *Nigella Sativa* 500 mg treatment on the mean±SEM scores of objective signs of protracted abstinence in 25 opioid addicts after every week during 12 weeks of follow up. Statistics comparing change in signs from pre-treatment in patient day-3 to week-12 indicated trend of decrease in signs to be reported on week-12 of follow up.

Figure-4: Effects of *Nigella sativa* 500 mg Treatment on Objective Signs of Protracted Abstinence in patients with Opioid Dependence during 12 weeks of Follow up

DISCUSSION

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.[1] 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.[6]

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 one heroin and other illicit drugs though much less frequently than before they entered treatment.[7] 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.[5]

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 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, JPMC, Karachi, in which role of calcium channel blockers was observed in the treatment of opioid dependence syndrome. These studies were carried out by Baloch[35], Mahesar[36], Salat[37], and Ansari[38] in which effect of calcium channel blocker in treatment of opioid dependence was evaluated in animal and patients.Baloch[35] and Mahesar[36] 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[37], 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 amitryptyline and thioridazine. Second clinical study was done by Ansari[38] 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 500 mg three times daily, *Nigella sativa* 500 mg reduced the subjective symptoms from pre-treatment day-3 scoring rate of 63.2±13.57 to14.56±8.13 at day-12. Similarly, objective signs were also reduced from pre-treatment day-3 scoring rate of 25.52±3.08 to 7.72±2.35 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. Maintenance with opioid agonists methadone or L-α-methadol (LAAM), antagonist (naltrexone) or partial agonist (buprenorphine) 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 *in vitro* studies that calcium channels/blockers modulate the opioid receptors or release of endogenous opiopeptins in one or other way.[39]

We found only one in vivo study[33], 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 was 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 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[25], along with analgesic, spasmolytic, anti-microbial, and anti-diarrhoeal etc., effects so this drug was used in this study.

CONCLUSION

For centuries**,** man has used plants for their healing properties .these plants play a fundamental part in all treatment modalities, both ancient and modern .the gentle, nourishing, and synergistic actions of herbal medicine make it an excellent treatment of choice for all systems 60. 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. Keeping in view the mode of action of opioids, pharmacological effects of *Nigella sativa* and results of present study, it is concluded that *Nigella sativa* is an effective treatment of opioid dependence. It is cheap and readily available and far more less in cast than other drugs presently available for the treatment of opioid withdrawal syndrome. Its antiallergic, anti bacterial, spasmolytic and antinociceptive effects and nutritious rich amino acids are more than of a benefit to an opioid addict, who usually requires these remedies and nutrious supplements. It is advised to conduct more research on this valuable seed in relation to its pharmacological potential.

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