Opioid dependence and substitution therapy: thymoquinone as potential novel supplement therapy for better outcome for methadone maintenance therapy substitution therapy

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ABSTRACT

Methadone is widely being used for opioid substitution therapy. However, the administration of methadone to opioid dependent individual is frequently accompanied by withdrawal syndrome and chemical dependency develops. Other than that, it is also difficult to retain patients in the treatment programme making their retention rates are decreasing over time. This article is written to highlights the potential use of prophetic medicines, Nigella sativa, as a supplement for opioid dependent receiving methadone. It focuses on the potential role of N. sativa and its major active compound, Thymoquinone (TQ) as a calcium channel blocking agent to reduce withdrawal syndrome and opioid dependency.

Keywords: Calcium channel blocker Methadone Nigella sativa Opioid dependence Thymoquinone

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Introduction

Methadone is the first widely used drug to overcome the opioid withdrawal effects (1, 2). It acts by occupying the receptor affected by exogenous opioids leading to subsequent receptor activation. Two channels are responsible for opioid withdrawal syndrome, calcium and potassium channel. This activation leads to closing of voltage-sensitive calcium channel (VSCC) and stimulation of potassium efflux causing hyperpolarization and inhibition of adenylyl cyclase activity (3, 4).

Successful approaches to pharmacotherapy in opioid addiction continue to rely largely on substitution of short-acting agonists such as heroin and oral administration of long acting high-efficacy agonists (methadone) or partial agonists (buprenorphine) (5, 6). Notably, all opioids that produce analgesia also can cause tolerance, addiction and withdrawal, and all of the available opioids are misused (7). It was shown that patients on long-term methadone maintenance treatment had longer QTc interval values than expected. Withdrawal symptoms among methadone maintenance therapy (MMT) patients had been reported to become worse and last longer than those of heroin or morphine due to extremely longer methadone half life (8). Low patient’s retention rates in the MMT programme was also reported, making them prone to re-injecting behaviour (9-11).

We believe that calcium channel blocking effect may play a crucial role in opioid dependent and withdrawal syndromes as shown by L-type voltage-dependent calcium antagonist role such as verapamil and felodipine in controlling the withdrawal syndromes effectively (12-15). Both central and peripheral mechanisms play an important role in attenuating opioid withdrawal syndrome via calcium channel blocking agents (16). The effects produced by calcium channel blockers are proven to be independent from opioid receptor sites as there is no agents that can replace naloxone from its binding sites (17). One study has reported that blockade of L-type voltage-dependent calcium channels by calcium channel blockers is responsible for the attenuation of morphine withdrawal (18). Other than that, T-type voltage dependent calcium channels have also been shown to play a critical role in the development of morphine dependence and withdrawal (19).

Previous study reported medicinal plants, Nigella sativa, a scientific name for Islamic Prophetic
medicine, Habbatus Sauda to have L-type calcium channel blocking effect (20). Moreover, further study had also introduced its seeds as a novel treatment for opioid dependence and proven effective in long term treatment of opioid dependence (21).

This plant has green to blue flowers with small black seeds and grows natively in temperate and cold climate areas. The seed of N. sativa possesses a source of the main active ingredients such as thymoquinone, monotropens-like P-cymene and α-pinene, nigelidene, nigellimine, and saponin (22-26).

Considering its low toxicity (27-29), we hypothesized that the main active compound of N. sativa, Thymoquinone (TQ), has a role in treating opioid withdrawal syndrome. Many therapeutic potential of TQ have been reported in a variety of medical conditions. TQ also exhibits calcium channel blocker properties via gut spasmolytic, tracheal, and airway relaxant, vasodilator and relaxant activities on the cardiac muscles (30). Thus, further study is needed in order to explore the biochemical effects and mechanism of action of N. sativa at cellular level.

**Conclusion**

As a conclusion, we would like to suggest probably with the supplementation of N. sativa to methadone, it will indirectly be a starting point to answer the question of opioid dependency and withdrawal for better retention of patients in MMT.

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**References**

1. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev 2003; 2:CD002209.
2. Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. Mount Sinai J Med, New York 1999; 67:347-364.
3. McDonald J, Lambert D. Opioid receptors. Continuing Education in Anaesthesia, Critical Care & Pain 2005; 5:22-25.
4. Xia M, Guo V, Huang R, Shahane SA, Austin CP, Nirenberg M, et al. Inhibition of morphine-induced cAMP overshoot: a cell-based assay model in a high-throughput format. Cell Mol Neurobiol 2011; 31:901-907.
5. Morgan MM, Christie MJ. Analysis of opioid efficacy, tolerance, addiction and dependence from cell culture to human. Br J Pharmacol 2011; 164:1322-1334.
6. Lohmayer P, Gossop M, Waal H, Bramness J. The pharmacological treatment of opioid addiction – a clinical perspective. Eur J Clin Pharmacol 2010; 66:537–545.
7. Yang F, Lin P, Li Y, He Q, Long Q, Fu X, et al. Predictors of retention in community-based methadone maintenance treatment program in Pearl River Delta, China. Harm Reduct J 2013; 10:10–1186.
8. Zhang L, Chow EP, Zhuang X, Liang Y, Wang Y, Tang C, et al. Methadone maintenance treatment participant retention and behavioural effectiveness in China: a systematic review and meta-analysis. Plos One 2013; 8:e69906.
9. Hernandez SH, Nelson LS. Prescription drug abuse: insight into the epidemic. Clin Pharmacol Ther 2010; 88:307–317.
10. Maremmani I, Pacini M, Cesaroni G, Lovrecic M, Perugi G, Tagliamonte A. QTc interval prolongation in patients on long-term methadone maintenance therapy. Eur Addict Res 2005; 11:44-49.
11. Mohamad N, Bakar N, Musa N, Talib N, Ismail R. Better retention of Malaysian opiate dependents treated with high dose methadone in methadone maintenance therapy. Harm Reduct J 2010; 7:30.
12. Ansari MA. To compare the role of calcium channel blocker with approved drugs used in opioid abstinence syndrome. [PhD Thesis]. Pakistan: Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi; 1999.
13. Baloch H. Role of verapamil in opioid dependence [PhD Thesis]. Pakistan: Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi; 1991.
14. Salat Y. Role of calcium channel blocker (verapamil) in acute opioid abstinence syndrome [PhD Thesis]. Pakistan: Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi; 1998.
15. Mahesar Z. Evaluation of the detoxifying role of felodipine in opioid dependence [PhD Thesis]. Pakistan: Department of Pharmacology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi; 1994.
16. Baeyens JM, Esposito E, Ossowska G, Samanin R. Effects of peripheral and central administration of calcium channel blockers on the naloxone precipitated abstinence syndrome in morphine dependent rats. Eur J Pharmacol 1987; 137:9–13.
17. Bongianni F, Carla V, Moroni F, Pellegrini, Giampietro DE. Calcium channel inhibitors suppress the morphine withdrawal syndrome in rats. Br J Pharmacol 1986; 88:561–567.
18. Mahani SE, Fathi Y, Motamed F, Hosseinpanah F, Ahmadzian A. L-type calcium channel blockade attenuates morphine withdrawal: In vivo interaction between L-type calcium channels and corticosterone. Horm Behav 2008; 53:351–357.
19. Dogrul A, Zagli U, Tulunay FC. The role of T-type calcium channels in morphine analgesia, development of antinociceptive tolerance and dependence to morphine, and morphine abstinence syndrome. Life Sci 2002; 71:725–734.
20. Gilani AH, Aziz N, Khurram IM, Chaudhry KS, Iqbal A. Bronchodilator, spasmylolic and calcium antagonist activities of Nigella sativa seeds (Kalonji): a traditional herbal product with multiple medicinal uses. J Pak Med Assoc 2001; 51:115–120.
21. Sangi S, Ahmed SF, Channa MA, Ashfaq M, Mastoi SM. A new and novel treatment of opioid dependence:
Nigella sativa 500 mg. J Ayub Med Coll Abbottabad 2008;20:118-124.

22. El-Dakhaldyny M. Studies on the chemical constitution of egyptian Nigella sativa L. Seeds. (ii) the essential oil. Planta Med 1963; 11:465–470.

23. Atta UR, Malik SO, Sadiq Hasan S, Iqbal Choudhary, Ni CZ, Clardy J. Nigellidine, a new indazol alkaloid from seeds of Nigella sativa. J Res Inst 1995; 36:1993–1996.

24. Atta UR, Malik SO, Sultan S, Chaudhary I, Rehman HU. Nigellimine N-oxide, a new isoquinoline alkaloid from the seeds of Nigella sativa. Heterocycles 1985; 23:953–955.

25. Ansari AK, Sadiy HAS. Structural studies on a saponin isolated from the seeds of Nigella sativa. Phyto Chem 1989; 7:377-379.

26. Keyhanmanesh R, Bagban N, Nazemiyeh H, Mirzaei Babil F, Alipour MR, Ahmady M. The relaxant effects of different methanolic fractions of Nigella sativa on guinea pig tracheal chains. Iran J Basic Med Sci 2013; 16: 123.

27. Tissera M, Chandrika M, Serasinghe P, Tangavelu R. Toxicity study of Kaluduru (oil of Nigella sativa).” Ayurveda Sameeksha 1997.

28. Badary OA, Al-Shabanah OA, Nagi MN, Al-Bekairi AM, Elmazar M. Acute and subchronic toxicity of thymoquinone in mice. Drug Develop Res 1998; 44:56-61.

29. Zaoui A, Cherrah Y, Mahassini N, Alaoui K, Amarouch H, Hassar M. Acute and chronic toxicity of Nigella sativa fixed oil. Phytomedicine 2002; 9:69-74.

30. Ghayur MN, Gilani AH, Janssen LJ. Intestinal, airway, and cardiovascular relaxant activities of thymoquinone. Evid Based Complement Alternat Med 2012; 2012.