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CASE REPORT

Traditional Chinese medicine-facilitated treatments may relieve anxiety symptoms during drug switching from methadone to buprenorphine/naloxone for treating opioid dependence

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SUMMARY

This study investigated a 51-year-old married man with a history of heroin dependence who underwent methadone maintenance treatment for 7 years. He received traditional Chinese medicine (TCM)-facilitated treatments and switched from methadone to buprenorphine/naloxone. Strong anxiety symptoms were observed during the initial stage; therefore, we prescribed a combination of Chaihu-Shugan-San, Zhi Bai Di Huang and Chin-Gin-Kuan-Ming decoction as the major herbal synergic regimen to relieve the symptoms of opioid withdrawal, anxiety and insomnia. During the treatment course, no precipitating withdrawal syndromes were noted, and the subject was gradually relieved of his anxiety symptoms through continual TCM treatments. In conclusion, TCM is effective in facilitating the switch from methadone to buprenorphine/naloxone and relieving anxiety symptoms. Therefore, focus on TCM-facilitated treatments for heroin dependence should be increased.

BACKGROUND

Heroin use is associated with an increased loss of productivity, disruption of personal relationships, crime and violence, and the spreading of infectious diseases such as HIV and AIDS.¹ Methadone maintenance treatment (MMT) is the most extensively used treatment for heroin dependence. Previous studies have indicated that MMT effectively reduces illicit heroin use² and mortality in opioid users.³ An alternative treatment option is buprenorphine/naloxone (Suboxone) maintenance therapy, which has proven effective for reducing opioid use and opioid cravings.⁴ Although the avoidance of daily methadone visits renders buprenorphine more convenient for opioid users, switching from methadone to buprenorphine is challenging.

Safe and effective treatments for opioid dependence are currently being researched; one new approach is the use of traditional Chinese medicine (TCM). Past studies have reported that TCM is effective in relieving the acute symptoms of methadone withdrawal during dosage reduction in patients with opioid dependence.^{5,6} We here present a case with successful drug switching from methadone to Suboxone under TCM, while TCM provided substantial effects over relieving

of opioid withdrawal symptoms and anxiety symptoms.

CASE PRESENTATION

This paper presents the case of a 51-year-old married man with a 15-year history of heroin dependence. In 2003, at the age of 37, he began using heroin while employed as an agricultural worker. He began using heroin to help him alleviate tension while working, but he gradually developed physical and psychological dependence. During the subject's heavy heroin use over 6 years, opioid withdrawal symptoms including insomnia, spontaneous perspiration, yawning and fatigue were exhibited continually. As in many cases of substance use disorders, the high cost of heroin engendered severe financial stress in this subject.

With the support of his wife and under the direction of a friend, he admitted himself to the MMT clinic of Taipei City Hospital Yang Ming Branch in 2008. His methadone dosage was 80 mg of methadone per day initially, and fluctuated between 60 and 80 mg between 2008 and 2014. In 2015, he decided to have his dosage reduced because of the inconvenience of visiting the MMT clinic daily. He gradually developed withdrawal symptoms after the dosage of methadone had been decreased to 30 mg, including anxiety, depression, fatigue, yawning, insomnia and musculoskeletal pain, all of which were disruptive to the subject's ability to function in society and led to severe frustration. Therefore, his dosage was subsequently increased back to 80 mg.

TREATMENT

Under encouragement from his family, the subject attempted to reduce his dosage again during the Chinese New Year holiday in 2016. Because of his previous frustrating experience, the subject exhibited extreme nervousness towards the dosage reduction plan, resulting in severe anxiety symptoms. The gradual dosage reduction to 45 mg exacerbated the subject's withdrawal and severe anxiety symptoms. The subject was admitted to our TCM clinic for intervention in June 2016. Following the TCM-based theory, we prescribed a combination of Chaihu-Shugan-San (CSS), Zhi Bai Di Huang (ZBDW) and Chin-Gin-Kuan-Ming (CGKM) as the subject's major herbal synergic regimen (table 1).



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Novel treatment (new drug/intervention; established drug/procedure in new situation)

Table 1 Major herbal ingredients and its treatment targets based on TCM theory

| TCM treatment | Major herbal ingredients | Treatment effects under TCM theory | Potential side effects |
|---|---|---|------------------------|
| Chaihu-Shugan-San (CSS) | Per. Citri Reticulatae, Rx. Bupleuri, Rx. Chuanxiong, Fr. Aurantii, Rx. Paeoniae Alba, Fried Rx. Glycyrrhizae, Rz. Cyperi | To improve the flow of systemic Qi, to relieve the stagnation of liver Qi, to relieve depression and to provide analgesic effects | Headache, palpitation |
| Zhi Bai Di Huang (ZBDW) | Rx. Anemarrhenae, Cx. Phellodendri, Rx. Rehmanniae Preparata, Fr. Corni Shan, Rx. Dioscoreae, Poria, Cx. Moutan, Rz. Alismatis | Enriches yin, nourishes the essence of the liver and kidneys, and reduces deficiency fire | Chillness, diarrhoea |
| Chin-Gin-Kuan-Ming (CGKM) tablets (It is composed of Chai-Hu-Jia-Long-Gu-Mu-Li-Tang, Xiao-Chaihu-Tang and Wen-Dan-Tang.) | Chai-Hu-Jia-Long-Gu-Mu-Li-Tang: Rx. Bupleuri, Chinensis, Os Draconis, Concha Ostreae, Rx. Ginseng, Sclerotium Poriae Cocos, Rx. Scutellariae Baicalensis, Ramulus Cinnamomi Cassiae, Rz. Pinelliae Ternatae, Fr. Jujubae, Rx. et Rhizoma Rhei, Rz. Zingiberis Officinalis Recens Xiao-Chaihu-Tang: Rx. Bupleuri Chinensis, Rx. Scutellariae Baicalensis, Rz. Pinelliae Ternatae, Rx. Codonopsis Pilosulae, Fr. Jujubae, Rx. Glycyrrhizae Uralensis, Rz. Zingiberis Recens Wen-Dan-Tang: Rz. Pinelliae Preparata, Caulis Bambusae In Taenia, Fr. Aurantii Immaturus, Per. Citri Reticulatae, Rx. Glycyrrhizae Uralensis, Sclerotium Poriae Cocos, Rz. Zingiberis Recens, Fr. Jujubae | To promote Qi movement and to sedate and calm the spirit | Dizziness, nausea |

Cx., Cortex; Fr., Fructus; Per., Pericarpium; Rx., Radix; Rz., Rhizoma; TCM, traditional Chinese medicine.

His acute methadone withdrawal symptoms and anxiety gradually reduced.

During the period in which the subject's methadone dosage was reduced from 45 to 3 mg, he did not experience severe opioid withdrawal symptoms as he had previously (figure 1).

The patient discontinued MMT in December 2016 after successfully switching to Suboxone (4mg/day) without precipitating withdrawal symptoms and only minor opioid withdrawal symptoms with slight dizziness and psychological discomfort. His

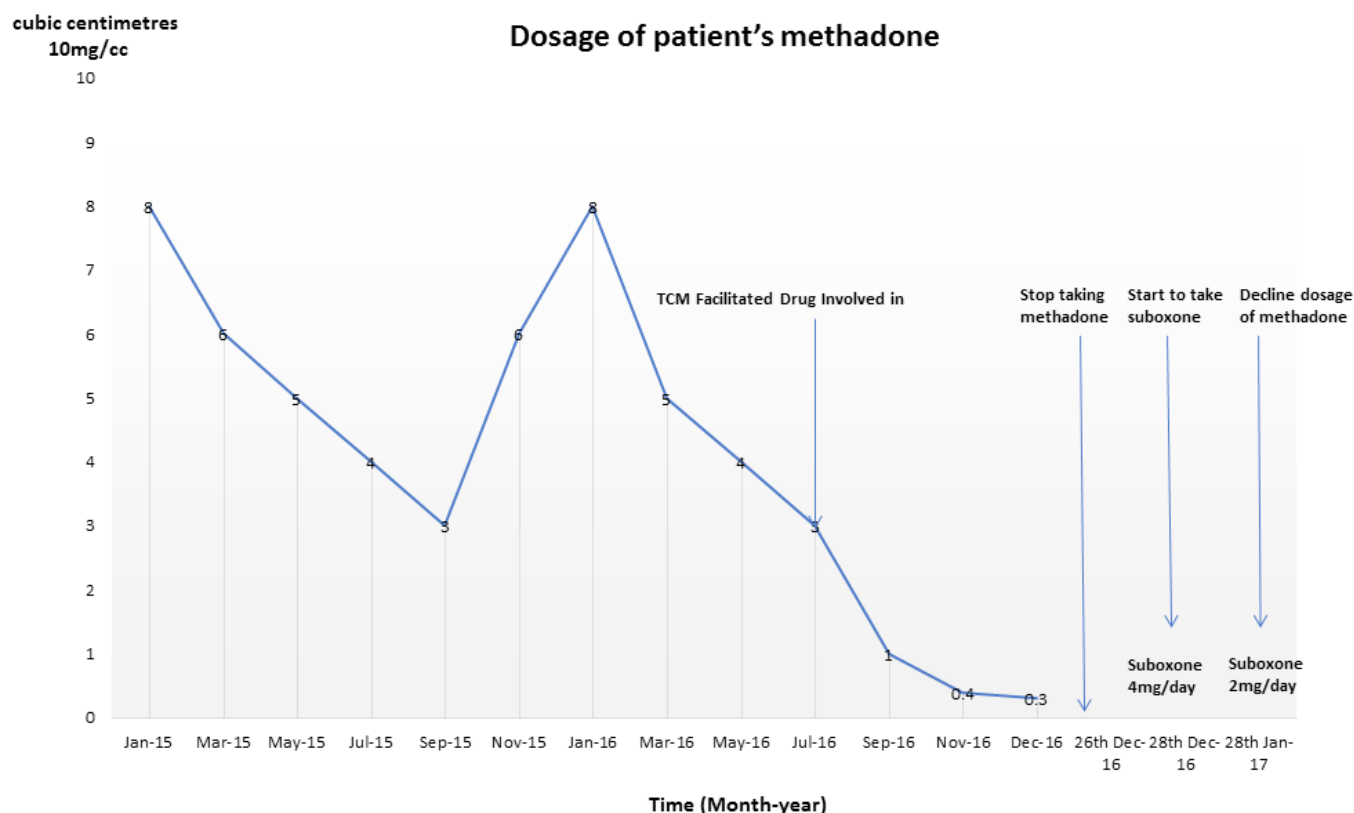


Figure 1 Patient did not reduce the dosage of methadone smoothly in 2015, but succeed in lowering the dosage after traditional Chinese medicine (TCM)-facilitated treatment administration in April 2016.

Suboxone dosage was reduced to 2mg in January 2017 and maintained in the following months.

OUTCOME AND FOLLOW-UP

From June 2016 to January 2017, the subject was treated with continuous TCM and successfully switched from methadone to Suboxone. The TCM will be maintained for at least a year. During follow-up examinations, unscheduled urine drug screenings were conducted four times, indicating no heroin use on all four occasions. TCM-facilitated treatment reduced the subject's withdrawal symptoms and enabled him to develop the confidence to live a life without heroin.

DISCUSSION

Opioid use disorder is a complex disorder involving physiological, psychological, genetic, behavioural and environmental factors.⁷ Opioid replacement treatments such as methadone and buprenorphine/naloxone can alleviate opioid withdrawal symptoms, reduce opioid cravings,⁸ reduce drug use and mortality due to opioid use and improve quality of life.⁹ In 2006, MMT was initially developed in Taiwan after an HIV/AIDS outbreak among heroin users.^{10 11} However, switching treatment drug from methadone to buprenorphine is challenging for people with heroin dependence, who may experience discomforting methadone withdrawal syndrome such as anxiety, irritability, insomnia and other opioid withdrawal symptoms. Therefore, ancillary counselling and medications, such as gamma aminobutyric acid receptor agonists, may provide substantial clinical effects.^{12–15}

In this case, the subject did not complete his first methadone dosage reduction attempt smoothly in 2015. His anticipatory anxiety led to a maladaptive focus on negative cognitions.^{16 17} However, encouraged by the strong family support, societal functionality and lack of any major active mental illnesses, we helped the patient switch from methadone to buprenorphine by prescribing TCM, with a strong focus on relieving his opioid withdrawal symptoms and controlling his anxiety symptoms.

We prescribed a combination of CSS, ZBDW and CGKM. The patient responded well to the treatments, exhibiting a gradual reduction of his opioid withdrawal symptoms and anxiety symptoms. In vitro experiments have indicated that the aforementioned herbal regimen may be effective for controlling depression and anxiety. One study indicated that Wen-Dan-Tang (WDT), a major component of CGKM, significantly reduced anxiety and prevented ghrelin level reduction due to sleep deprivation in the study subject, especially in the hypothalamus, thereby suggesting that the mechanism of WDT may correspond to changes in the brain-gut axis.¹⁸ CSS has antidepressant-like effects and was mediated by reversing the stress-induced disruption of ERK5 expressions in the hippocampi of rats.¹⁹ CGKM tables were composed of Chai-Hu-Jia-Long-Gu-Mu-Li-Tang, Xiao-Chaihu-Tang and WDT. Xiao-Chaihu-Tang was able to significantly regulate depression-like and anxiety-like behaviours induced by chronic social isolation stress, which is likely attributed to the promotion of hippocampal neurogenesis and neurotrophin expressions through the activation of the serotonergic system.²⁰

In conclusion, intensive control of anxiety symptoms in the case of the present study was a key factor in the subject successfully reducing his methadone dosage and switching to buprenorphine/naloxone. In addition, TCM proved effective

for alleviating discomforts such as depression, fatigue and musculoskeletal pain during the initial methadone withdrawal period, and reduced the chances of precipitating withdrawal symptoms induced by buprenorphine/naloxone treatment. Furthermore, we have also set up a non-stigmatised therapeutic environment for the case and the clinical staff have provided supportive and empathetic attitude during the follow-ups. Further research should focus on the application of TCM for individuals with heroin dependence during the period of switching from methadone to buprenorphine/naloxone.

Patient's perspective

I am very grateful to the assistance of Chinese medicine to switch from methadone to Suboxone, so I do not have to go to the hospital every day to take methadone and make me relaxed, then I hope to quit the Suboxone, being a completely normal person.

Learning points

- Methadone maintenance treatment is a replacement therapy for heroin dependence.
- Traditional Chinese medicine may relieve the withdrawal syndrome of methadone maintenance treatment including anxiety and depression.
- Offering support and affirmation may also play an important role to switch from methadone to Suboxone.

Contributors KCY took care of the whole TCM procedure of treating the patient, and accepted the advice on paper direction from CHH for writing the paper. HTW took care of the whole methadone medicine treatment of the patient, and gave the information of methadone dosage. YHY offered support and affirmation to the patient. CHH gave great advice on drafting the structure of the paper, and the direction of treatment.

Competing interests None declared.

Patient consent Obtained.

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REFERENCES

- 1 Zhu JW, Liu FL, Mu D, et al. Heroin use is associated with lower levels of restriction factors and type I interferon expression and facilitates HIV-1 replication. *Microbes Infect* 2017;19:288–94.
- 2 Coplehorn JR, Dalton MS, Haldar F, et al. Methadone maintenance and addicts' risk of fatal heroin overdose. *Subst Use Misuse* 1996;31:177–96.
- 3 Darke S, Swift W, Hall W, et al. Predictors of injecting and injecting risk-taking behaviour among methadone-maintenance clients. *Addiction* 1994;89:311–6.
- 4 Giacomuzzi SM, Riemer Y, Ertl M, et al. Buprenorphine versus methadone maintenance treatment in an ambulant setting: a health-related quality of life assessment. *Addiction* 2003;98:693–702.
- 5 Wang X, Li J, Huang M, et al. A study on Fu-Yuan Pellet, a traditional Chinese medicine formula for detoxification of heroin addictions. *Am J Drug Alcohol Abuse* 2009;35:408–11.
- 6 Kang L, Li B, Gao L, et al. Tai-Kang-Ning, a Chinese herbal medicine formula, alleviates acute heroin withdrawal. *Am J Drug Alcohol Abuse* 2008;34:269–76.
- 7 Canadian Agency for Drugs and Technologies in Health. *Buprenorphine/Naloxone Versus Methadone for the Treatment of Opioid Dependence: A Review of Comparative*

- Clinical Effectiveness, Cost-Effectiveness and Guidelines*[Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2016. https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089424/pdf/PubMedHealth_PMH0089424.pdf.
- 8 Hser YI, Evans E, Huang D, *et al*. Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial. *Addiction* 2016;111:695–705.
 - 9 Pihkila H, Sandlund M. Parenthood and opioid dependence. *Subst Abuse Rehabil* 2015;6:33–40.
 - 10 Tang YL, Zhao D, Zhao C, *et al*. Opiate addiction in China: current situation and treatments. *Addiction* 2006;101:657–65.
 - 11 Lyu SY, Su LW, Chen YM. Effects of education on harm-reduction programmes. *Lancet* 2012;379:e28–e30.
 - 12 Mannelli P, Peindl KS, Lee T, *et al*. Buprenorphine-mediated transition from opioid agonist to antagonist treatment: state of the art and new perspectives. *Curr Drug Abuse Rev* 2012;5:52–63.
 - 13 van Niel JC, Schneider J, Tzschenke TM. Efficacy of Full μ -Opioid Receptor Agonists is not Impaired by Concomitant Buprenorphine or Mixed Opioid Agonists/Antagonists - Preclinical and Clinical Evidence. *Drug Res* 2016;66:562–70.
 - 14 Barry DT, Fazzino T, Necrason E, *et al*. The Availability of Ancillary Counseling in the Practices of Physicians Prescribing Buprenorphine. *J Addict Med* 2016;10:352–6.
 - 15 Johnson RE, Strain EC, Amass L. Buprenorphine: how to use it right. *Drug Alcohol Depend* 2003;70:S59–S77.
 - 16 Karsinti E, Fortias M, Dupuy G, *et al*. Anxiety disorders are associated with early onset of heroin use and rapid transition to dependence in methadone maintained patients. *Psychiatry Res* 2016;245:423–6.
 - 17 Engelmann JB, Meyer F, Fehr E, *et al*. Anticipatory anxiety disrupts neural valuation during risky choice. *J Neurosci* 2015;35:3085–99.
 - 18 Wang L, Song Y, Li F, *et al*. Effects of Wen Dan Tang on insomnia-related anxiety and levels of the brain-gut peptide Ghrelin. *Neural Regen Res* 2014;9:205–12.
 - 19 Qiu J, Hu SY, Zhang CH, *et al*. The effect of Chaihu-Shugan-San and its components on the expression of ERK5 in the hippocampus of depressed rats. *J Ethnopharmacol* 2014;152:320–6.
 - 20 Ma J, Wu CF, Wang F, *et al*. Neurological mechanism of Xiaochaihutang's antidepressant-like effects to socially isolated adult rats. *J Pharm Pharmacol* 2016;68:1340–9.

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