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The effects of Tranquival tablet on some heroin withdrawal symptoms

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Original Article

Abstract

BACKGROUND: Individuals, during opioid withdrawal period, experience symptoms such as dysphoria, insomnia, anxiety, irritability, nausea, agitation, tachycardia, and hypertension which may trigger drug seeking behavior and relapse. This study was conducted with the aim of determining the effect of Tranquival tablets on some heroin withdrawal symptoms in addicted patients referred to an outpatient clinic.

METHODS: In this single-blind quasi-experimental study, 69 patients (37 patients in intervention group and 32 in control group) suffering from heroin withdrawal syndrome were allocated randomly to study groups. In the intervention group, 1 Tranquival tablet was administered 1 hour before sleeping each night for 6 weeks. In the control group, 1 tablet of clonazepam (1 mg) was administered at the same time. The Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Rating Scale (HAM-A), and visual analogue scale (VAS) were completed at the beginning, 3 weeks later, and the end of the study. Data were analyzed using Student's t-test, repeated measures analysis, and chi-square test.

RESULTS: During the study period in both groups, withdrawal symptoms significantly decreased ($P < 0.001$); however, this difference was insignificant between the 3 assessment steps ($P > 0.050$). Furthermore, the Bonferroni correction showed an relationship between Tranquival and clonazepam groups in terms of mean anxiety at the begining and the end stage of assessment ($P = 0.012$). However, these relationships were insignificant in terms of mean sleep and muscular pain ($P = 0.153$ and $P = 0.267$, respectively).

CONCLUSION: Tranquival was as effective as clonazepam in the reduction of muscular pain and anxiety, and improvement of sleep quality in patients suffering from heroin withdrawal syndrome.

KEYWORDS: Clonazepam, Heroin Dependence, Substance Withdrawal Syndrome

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Introduction

Heroin is one of the most commonly used drugs among drug users in both developed and developing countries. Methadone maintenance treatment (MMT) has been found to be an effective harm reduction program for drug users.[1] Methadone is a long-acting synthetic opioid with high attraction to various opioid receptors and has been used as a successful pharmacologic treatment for patients with heroin dependency, and acute and chronic pain.[2] However, there are few studies which comparatively examined the development and course of withdrawal symptoms in opiate addicts in response to such detoxification procedures.[3] Individuals, during the opioid withdrawal period, experience symptoms such

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as dysphoria, insomnia, anxiety, irritability, nausea, agitation, tachycardia, and hypertension which may trigger drug-seeking behavior and relapse.[4]

Drugs such as benzodiazepines are administered in the treatment of heroin withdrawal symptoms.[5] In MMT programs, patients who are addicted to benzodiazepine are at risk for polydrug abuse.[6] Most patients relapse to opioids within one month of opioid agonist detoxification; therefore, there is low rate of completion of detoxification.[7] Some evidence indicates that drugs which are often used to treat anxiety and insomnia have adverse effects that are related to acquired tolerance and withdrawal from the drug.[8,9]

Today, herbal remedies are a popular form of therapy and have been developed as alternative methods of inducing calming effects.[10] Tranquival is an herbal product which consists of valerian, Passiflora, Melissa officinalis, and Humulus lupulus. The efficacy of its ingredients in different disorders has been previously demonstrated. Passiflora is effective on treating nervous restlessness, sleep disorders, nervous stress, generalized anxiety disorder (GAD), symptoms of opiate withdrawal, insomnia, neuralgia, convulsion, spasmodic asthma, attention deficit hyperactivity disorder (ADHD), palpitations, cardiac arrhythmia, hypertension, sexual dysfunction, and menopause.[11-16] Valeriana officinalis L. is a member of the Valerianaceae family with hypnotic,[17] anxiolytic,[18] antidepressant, and myorelaxant properties.[19] Melissa officinalis L. (lemon balm) is used in traditional medicine to treat insomnia, anxiety, gastric conditions, psychiatric conditions, migraine, hypertension, mild to moderate bronchial conditions, and sleep disturbances.[20,21] Humulus lupulus L. (hop) is well known throughout the world, and is used as a mild sedative and activator of gastric function.[22]

Despite the increasing interest in natural and complementary therapies for substance use disorders, clinical studies in this area are limited and there are insufficient documents to support the use of these therapies for opiate withdrawal symptoms. The present study was conducted with the aim of determining the effect of Tranquival on some opiate withdrawal symptoms in heroin addicted patients in the detoxification phase.

Materials and Methods

This study was conducted in an addiction treatment clinic, in Shahrekord, Iran (from June 2012 until October 2012). The Ethics Committee of Shahrekord Univeristy of Medical Sciences, Shahrekord, approved the study protocol and the study was registered in the Iranian Clinical Trial Center (IRCT) by IRCT201306222085N10.

Written informed consents were obtained from all patients before entering the study. A psychiatrist visited all patients and carried out the diagnosis of opioid withdrawal. This psychiatrist prescribed Tranquival or clonazepam for the patients in different study groups.

In this quasi-experimental study, the participants consisted of 80 males with a history of heroin addiction. The participants fulfilled the criteria for opioid dependency and withdrawal syndrome of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR). All subjects were outpatients who referred to an addiction treatment clinic. Inclusion criteria consisted of age of 20 to 50 years, a history of heroin use of at least 2 years (0.5 to 1 gr/day), suffering from withdrawal syndrome, receiving methadone treatment (30 to 60 mg/day), lack of allergy to Passiflora, Valeriana officinalis, Humulus lupulus, and Melissa officinalis, and referring to an addiction treatment clinic. Exclusion criteria consisted of psychiatric disorders or history of hospitalization in a psychiatric ward, unwillingness to participation in the study, and occurrence of any side effects related to

Tranquival consumption. In addition, patients who used opioids or drugs without the prescription of a psychiatrist were excluded from the study.

A number was given to each patient, then, according to their odd or even numbers, they were randomly assigned to Tranquival (n = 40) or clonazpam (n = 40) groups.

In the present study, a general physician who was not aware of the patients' groups completed the study questionnaires; thus, this study was a single-blind study. In addition, regarding to the different shapes of Tranquival and clonazepam tablets, the patients were aware of their medication type.

In the Tranquival (intervention) group, the patients took 1 tablet of Tranquival (Dineh Iran Co., Iran) orally an hour before sleep every night for 6 weeks. The ingredients of the Tranquival tablet are 150 mg Valeriana officinalis, 100 mg Passiflora incarnata, 50 mg Humulus lupulus, and 50 mg Melissa officinalis. In the clonazepam (control) group, the patients took 1 mg of clonazepam (Arya Co., Iran) orally an hour before sleep every night for 6 weeks.

The data collection tools consisted of the Pittsburgh Sleep Quality Index (PSQI), Hamilton Anxiety Rating Scale (HAM-A), and visual analogue scale (VAS) for muscular pain assessment. The questionnaires were completed in 3 steps; at the beginning of the study (T1), and 3 (T2) and 6 weeks later (T3). The PSQI is a standardized self-administered questionnaire. Its reliability and validity have been approved for patients with psychiatric disorders, sleep disturbance, and other somatic diseases.[23] The PSQI consists of 7 clinically derived components that assess sleep difficulty, and the sum of these component scores yields a global score of subjective sleep quality (range: 0–21). The reliability and validity of the Persian version of the PSQI (PSQI-P) were assessed by Farrahi et al.[24] In the study by Farrahi et al., the sensitivity and specificity of discrimination of patients with insomnia from control subjects was 94% and 72% for a PSQI cut-off value of 5, and 85% and 84% for a PSQI cut-off value of 6, respectively. The psychometric properties of the PSQI-P are acceptable.[24]

The HAM-A is one of the first rating scales developed to measure the severity of anxiety symptoms, and is widely used in both clinical and research setting. The scale consists of 14 items, each defined by a series of symptoms, and measures of both psychic and somatic anxiety. The HAM-A is widely used as an outcome measure in clinical trials. The reported levels of reliability for the scale are acceptable. Each item is scored on a scale of 0 (not present) to 4 (severe), with a total score range of 0–56. A score of lower than 17 indicates mild severity, 18–24 mild to moderate severity, and 25–30 moderate to severe.[25] This scale was used in an Iranian study.[13] HAM-A consists of 14 factors. A validity of 75% and reliability of 85% has been reported for this scale by Divsalar et al.[26]

The reliability of the VAS for acute pain measurement is high and the VAS is sufficiently reliable in the assessment of acute pain.[27] The VAS is a self-report questionnaire. The respondent is asked to place a line perpendicular to the VAS line at the point that represents their pain intensity. In clinical practice, the percentage of pain relief which is assessed by VAS is considered as a measure of the efficacy of treatment. A higher score indicates greater pain intensity. The reliability and validity of the VAS for disability in patients with chronic musculoskeletal pain has been evaluated by Boonstra et al.[27]

In the present study, data were statistically analyzed using SPSS software (version 16, SPSS Inc., Chicago, IL, USA) and Student's t-test, repeated measures analysis (Bonferroni correction), and chi-square test.

Results

There were no significant differences between the two study groups in terms of the history of addiction in close family members, educational level, economic status, occupation, marital status, age, and heroin dependency period (Table 1). Over the course of the trial, 3 subjects dropped out from the Tranquival group and 8 from the clonazepam group. Therefore, 37 patients in the Tranquival group and 32 in the clonazepam group completed the trial (Figure 1).

Table 1. Demographic characteristics of patients in the two study groups

Variables		Tranquival group	Clonazepam group	P
Occupation	Employed	20	20	0.62
	Unemployed	17	12	
Marital status	Single	13	8	0.43
	Married	24	24	
History of addiction in family	No	24	16	0.23
	Yes	13	16	
Education	Illiterate	16	10	0.28
	Primary school	16	13	
	Middle and high school	5	9	
Economic status	Sufficient	16	10	0.33
	Insufficient	21	22	
Age (year)		31.40 ± 8.30	34.80 ± 8.00	0.09
Heroin dependency period (year)		3.62 ± 1.44	3.25 ± 0.95	0.20

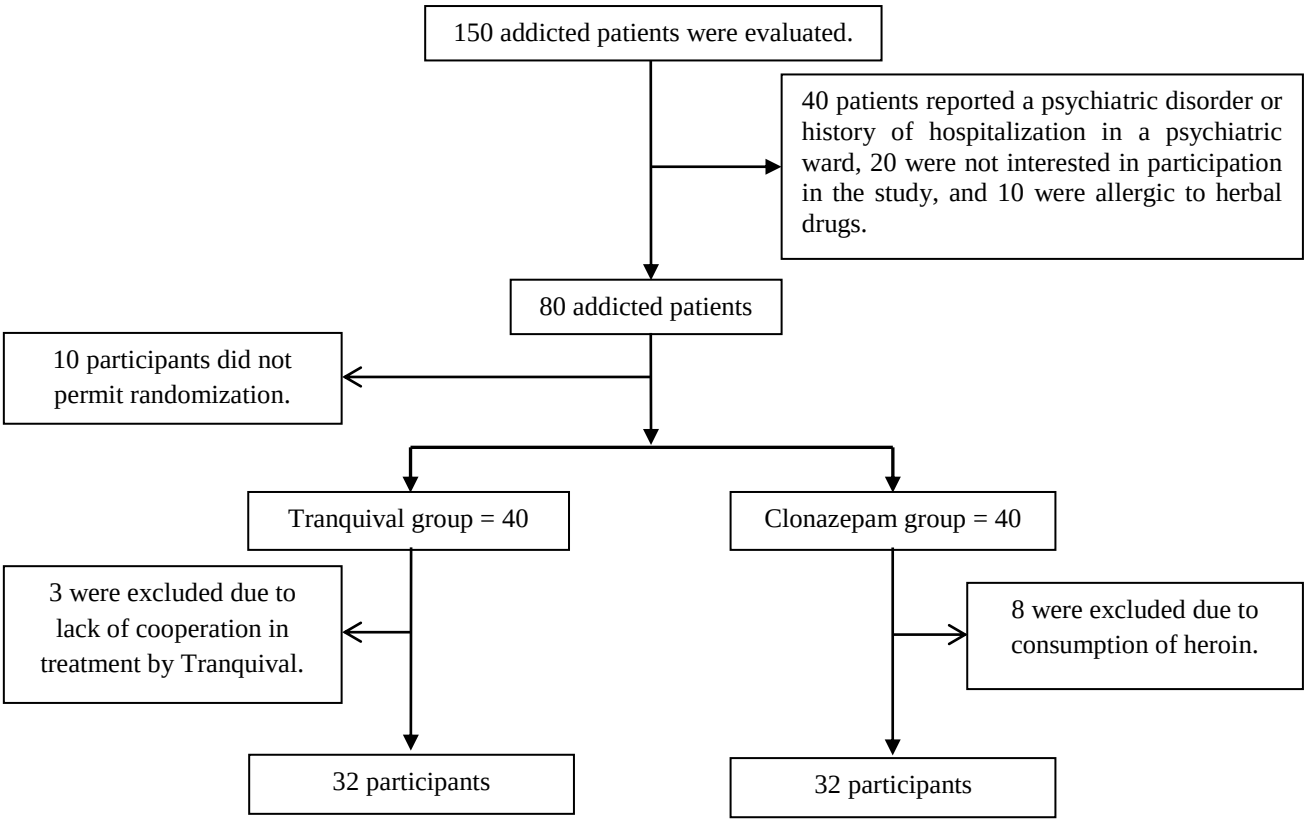

Figure 1. Flow chart of study participants

Table 2. Comparison of the anxiety, quality of sleep, and muscular pain scores in different stages of the study among the two groups

Symptom	Stage of assessment	Tranquival group (mean ± SD)	Clonazepam group (mean ± SD)
Anxiety	Before	23.9 ± 8.2	23.8 ± 8.1
	3 Weeks later	15.4 ± 6.6	17.0 ± 7.9
	6 Weeks later	13.0 ± 7.4	15.8 ± 7.7
Sleep	Before	14.2 ± 3.3	14.5 ± 3.3
	3 Weeks later	8.2 ± 3.1	9.7 ± 4.0
	6 Weeks later	7.4 ± 3.5	9.1 ± 4.5
Muscular pain	Before	51.0 ± 31.0	47.1 ± 30.7
	3 Weeks later	38.0± 28.8	34.3 ± 27.0
	6 Weeks later	28.4 ± 25.5	31.0 ± 25.4

Mean anxiety, sleep disorder, and muscular pain in both groups showed a descending trend (P < 0.001)
There was no significant differences between the two groups in the 3 assessment stages in terms of mean anxiety, sleep disorder, and muscular pain (P > 0.05); SD: Standard deviation

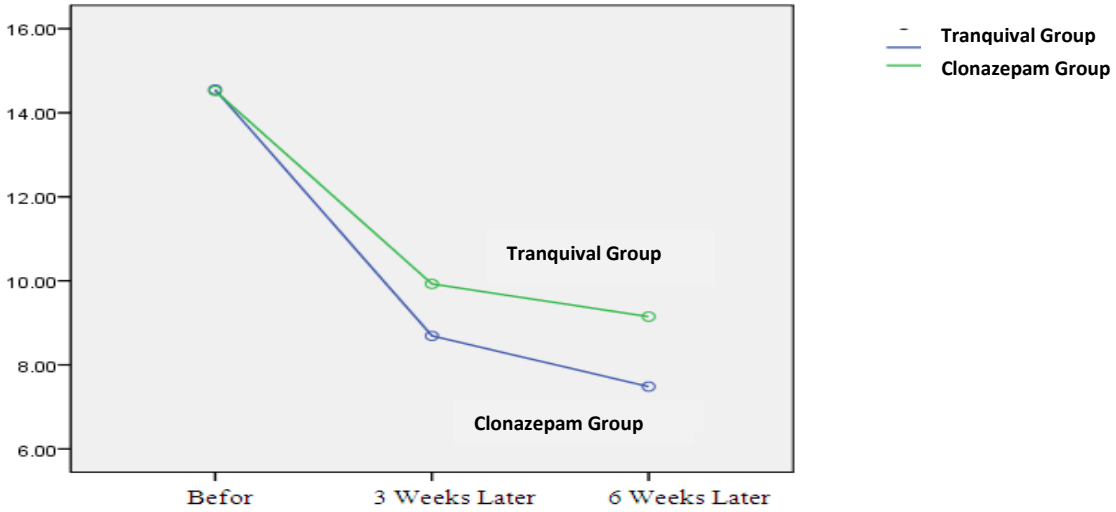

Figure 2. Comparison of the quality of sleep score in different stages of the study among the two groups

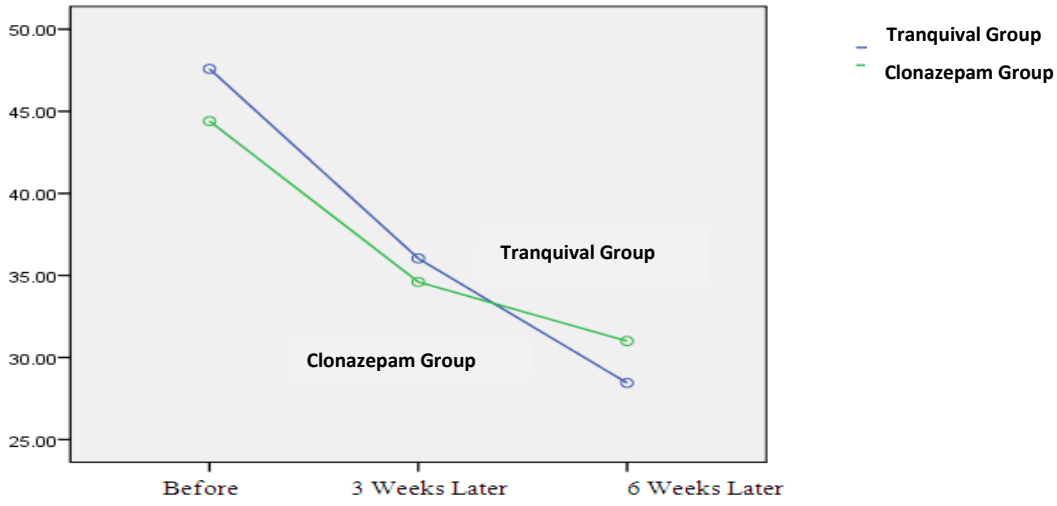

Figure 3. Comparison of muscular pain score in different stages of the study among the two groups

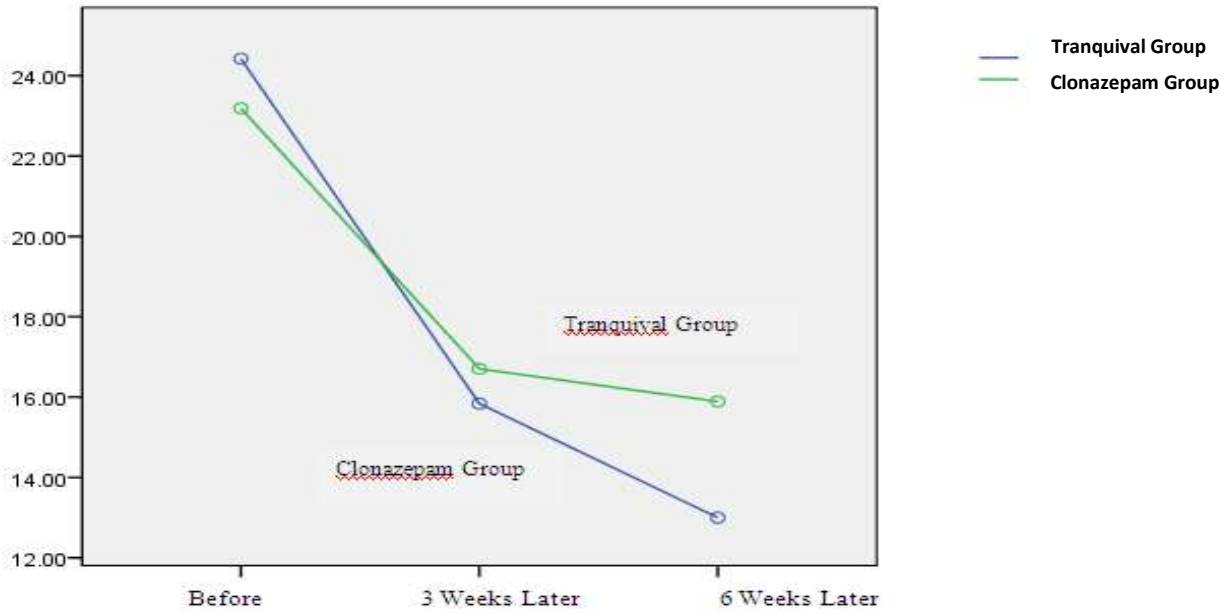

Figure 4. Comparison of the anxiety score in different stages of the study among the two groups

During the study period, in both groups, withdrawal symptoms (sleep, anxiety, and muscular pain) significantly decreased ($P < 0.001$) (Table 2); however, this difference was insignificant in the 3 assessment steps ($P > 0.050$). Furthermore, Bonferroni correction showed a relationship between Tranquival and clonazepam groups in mean anxiety at the beginning and the end stage of assessment ($P = 0.012$). Nevertheless, these relationships were insignificant in terms of mean sleep and muscular pain ($P = 0.153$ and $P = 0.267$, respectively) (Figures 2-4).

In both groups, patients reported drowsiness, but the rate of this side effect was higher in the clonazepam group (3 in Tranquival vs. 9 in clonazepam group). In addition, 3 patients in the clonazepam group had amnesia.

Discussion

This study showed that Tranquival was as effective as clonazepam in the treatment of some withdrawal symptoms in patients with heroin addiction in the detoxification phase. In addition, patients in the Tranquival group reported fewer side effects and greater compliance in comparison to the clonazepam group.

Treatment with benzodiazepines may reduce complaints of pain, but this seems to be an indirect effect related to their psychotropic properties, such as alleviation of anxiety and, in selected cases, depression. Clinical experience has shown benzodiazepines to be effective in the treatment of acute muscle spasm, concomitant chronic pain and anxiety, and lancinating neropathic pain, in which case clonazepam and alprazolam may be the agents of choice.[28]

Although a limited number of clinical studies have been performed on the effectiveness of Tranquival in treatment of opiate detoxification and withdrawal syndrome, each ingredient of Tranquival has anxiolytic effects. Melissa officinalis, Humulus lupulus (hops), valerian, and Passiflora incarnata inhibit γ-aminobutyric acid (GABA) catabolism.[12,29,30]

Miroddi et al., in a bibliographic investigation, found that the genus Passiflora incarnata has been used to cure subjects affected by opiate dependence in India.[31] b

and Conduit, suggested that the consumption of a low dose of Passiflora incarnata is effective in the treatment of mild sleep fluctuations in healthy adults.[15] Akhondzadeh et al. found Passiflora to be effective in the treatment of physical symptoms related to opiates withdrawal syndrome.[13] The numerous pharmacological effects of Passiflora incarnata are mediated via modulation of the GABA system, including affinity to GABAA and GABAB receptors and effects on GABA uptake.[14] In addition, valerian extract (valepotriates) has a potential anxiolytic effect on the psychic symptoms of anxiety. Andreatini et al. suggested that valepotriates have a potential anxiolytic effect on the psychic symptoms of anxiety.[32]

On the other hand, Melissa officinalis is effective on the treatment of anxiety and sleep disturbances. Guginski et al. found that Melissa officinalis (lemon balm) extract produced dose-related antinociceptive effect in several models of chemical pain with cholinergic mechanisms and the L-arginine-nitric oxide pathway. The rosmarinic acid in this plant contributes to its antinociceptive effect.[33]

The sedative effects of Humulus lupulus L. (hops) extract result mainly from its bitter acids, and in particular their oxidative degradation products such as that resulting from the α-acid content (2-methyl-3-buten-2-ol).[34] The main mechanism of action of hops is increasing the activity of the GABA neurotransmitter through modulation of brain GABA (A) receptors. The sedative effect of hops on the nervous system has been widely reported in animal research, as also has its narcotic effect at high concentrations due to 2-methyl-3.[35] Park et al., in their study, suggested that hop extract has an antinociceptive property in various pain models. Furthermore, the antinociceptive effect of hop extract may be mediated by opioidergic receptors.[35]

Furthermore, studies have shown that the combination of these herbs are effective in the treatment of anxiety and sleep disturbance. Kennedy et al. approved the anxiolytic effect of the combination of Melissa officinalis and valerian.[36] In addition, Wahling et al. showed that the combination of valerian, hops, and passion flower can increase sleep quality.[37].

Conclusion

Regarding the effectiveness of Tranquival in reduction of some withdrawal symptoms in heroin addicted patients in the detoxification phase and its fewer side effects in comparison to clonazepam, researchers suggested that this tablet be used in the treatment of heroin withdrawal symptoms. The efficacy of Tranquival may be related to different properties of its ingredients. However, further studies should be undertaken to determine the efficacy and the mechanism of action of Tranquival on withdrawal syndrome.

Conflict of Interests

Authors have no conflict of interests.

Acknowledgments

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References

1. Sun HM, Li XY, Chow EP, Li T, Xian Y, Lu YH, et al. Methadone maintenance treatment programme reduces criminal activity and improves social well-being of drug users in China: a systematic review and meta-analysis. BMJ Open 2015; 5(1): e005997.
2. Reingardiene D, Jodziuniene L, Lazauskas R. Methadone treatment and its dangers. Medicina (Kaunas) 2009; 45(5): 419-25.
3. Gossop M, Bradley B, Phillips GT. An investigation of withdrawal symptoms shown by opiate addicts during and subsequent to a 21-day in-patient methadone detoxification procedure. Addict Behav 1987; 12(1): 1-6.

4. Swift RM, Stout RL. The relationship between craving, anxiety, and other symptoms in opioid withdrawal. J Subst Abuse 1992; 4(1): 19-26.
5. Lintzeris N, Nielsen S. Benzodiazepines, methadone and buprenorphine: interactions and clinical management. Am J Addict 2010; 19(1): 59-72.
6. Bleich A, Gelkopf M, Weizman T, Adelson M. Benzodiazepine abuse in a methadone maintenance treatment clinic in Israel: characteristics and a pharmacotherapeutic approach. Isr J Psychiatry Relat Sci 2002; 39(2): 104-12.
7. Northrup TF, Stotts AL, Green C, Potter JS, Marino EN, Walker R, et al. Opioid withdrawal, craving, and use during and after outpatient buprenorphine stabilization and taper: a discrete survival and growth mixture model. Addict Behav 2015; 41: 20-8.
8. Busto U, Sellers EM. Pharmacologic aspects of benzodiazepine tolerance and dependence. J Subst Abuse Treat 1991; 8(1-2): 29-33.
9. Kavan MG, Elsasser G, Barone EJ. Generalized anxiety disorder: practical assessment and management. Am Fam Physician 2009; 79(9): 785-91.
10. Head KA, Kelly GS. Nutrients and botanicals for treatment of stress: adrenal fatigue, neurotransmitter imbalance, anxiety, and restless sleep. Altern Med Rev 2009; 14(2): 114-40.
11. Blumenthal M, Busse WR, Goldberg A. The complete German commission e monographs: therapeutic guide to herbal medicines. Philadelphia, PA: Elsevier Health Sciences; 1999.
12. Appel K, Rose T, Fiebich B, Kammler T, Hoffmann C, Weiss G. Modulation of the gamma-aminobutyric acid (GABA) system by Passiflora incarnata L. Phytother Res 2011; 25(6): 838-43.
13. Akhondzadeh S, Kashani L, Mobaseri M, Hosseini SH, Nikzad S, Khani M. Passionflower in the treatment of opiates withdrawal: a double-blind randomized controlled trial. J Clin Pharm Ther 2001; 26(5): 369-73.
14. Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther 2001; 26(5): 363-7.
15. Ngan A, Conduit R. A double-blind, placebo-controlled investigation of the effects of Passiflora incarnata (passionflower) herbal tea on subjective sleep quality. Phytother Res 2011; 25(8): 1153-9.
16. Cronin JR. Passionflower: Reigniting Male Libido and Other Potential Uses. Alternative & Complementary Therapies 2003; 9(2): 89-92.
17. Herrera-Arellano A, Luna-Villegas G, Cuevas-Uriostegui ML, Alvarez L, Vargas-Pineda G, Zamilpa-Alvarez A, et al. Polysomnographic evaluation of the hypnotic effect of Valeriana edulis standardized extract in patients suffering from insomnia. Planta Med 2001; 67(8): 695-9.
18. Murphy K, Kubin ZJ, Shepherd JN, Ettinger RH. Valeriana officinalis root extracts have potent anxiolytic effects in laboratory rats. Phytomedicine 2010; 17(8-9): 674-8.
19. Hattesohl M, Feistel B, Sievers H, Lehnfeld R, Hegger M, Winterhoff H. Extracts of Valeriana officinalis L. s.l. show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties. Phytomedicine 2008; 15(1-2): 2-15.
20. Hancianu M, Aprotosoaie AC, Gille E, Poiata A, Tuchilus C, Spac A, et al. Chemical composition and in vitro antimicrobial activity of essential oil of Melissa officinalis L. from Romania. Rev Med Chir Soc Med Nat Iasi 2008; 112(3): 843-7.
21. Cases J, Ibarra A, Feuillere N, Roller M, Sukkar SG. Pilot trial of Melissa officinalis L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. Med J Nutrition Metab 2011; 4(3): 211-8.
22. Zanoli P, Zavatti M. Pharmacognostic and pharmacological profile of Humulus lupulus L. J Ethnopharmacol 2008; 116(3): 383-96.
23. Carpenter JS, Andrykowski MA. Psychometric evaluation of the Pittsburgh Sleep Quality Index. J Psychosom Res 1998; 45(1): 5-13.
24. Farrahi MJ, Nakhaee N, Sheibani V, Garrusi B, Amirkafi A. Reliability and validity of the Persian version of the Pittsburgh Sleep Quality Index (PSQI-P). Sleep Breath 2012; 16(1): 79-82.
25. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32(1): 50-5.
26. Divsalar P, Shafiei Darbasiabi F, Nasehzadeh A, Divsalar K, Dehyadegary E. The Global Assessment function comparison in bipolar patients at mania episode and mixed episode and analysing the relationship between the anxiety and depression rate of these two groups of patients. Life Science Journal 2013; 10(12s): 1-7.
27. Boonstra AM, Schiphorst Preuper HR, Reneman MF, Posthumus JB, Stewart RE. Reliability and validity of the visual analogue scale for disability in patients with chronic musculoskeletal pain. Int J Rehabil Res 2008; 31(2): 165-9.
28. Reddy S, Patt RB. The benzodiazepines as adjuvant analgesics. J Pain Symptom Manage 1994; 9(8): 510-4.
29. Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL, Arnasona JT. Effects of traditionally used anxiolytic botanicals on enzymes of the ?-aminobutyric acid (GABA) system. Canadian Journal of Physiology and Pharmacology 2007; 85(9): 933-42.

30. Awad R, Muhammad A, Durst T, Trudeau VL, Arnason JT. Bioassay-guided fractionation of lemon balm (Melissa officinalis L.) using an in vitro measure of GABA transaminase activity. Phytother Res 2009; 23(8): 1075-81.
31. Miroddi M, Calapai G, Navarra M, Minciullo PL, Gangemi S. Passiflora incarnata L.: ethnopharmacology, clinical application, safety and evaluation of clinical trials. J Ethnopharmacol 2013; 150(3): 791-804.
32. Andreatini R, Sartori VA, Seabra ML, Leite JR. Effect of valepotriates (valerian extract) in generalized anxiety disorder: a randomized placebo-controlled pilot study. Phytother Res 2002; 16(7): 650-4.
33. Guginski G, Luiz AP, Silva MD, Massaro M, Martins DF, Chaves J, et al. Mechanisms involved in the antinociception caused by ethanolic extract obtained from the leaves of Melissa officinalis (lemon balm) in mice. Pharmacol Biochem Behav 2009; 93(1): 10-6.
34. Zanoli P, Rivasi M, Zavatti M, Brusiani F, Baraldi M. New insight in the neuropharmacological activity of Humulus lupulus L. J Ethnopharmacol 2005; 102(1): 102-6.
35. Park SH, Sim YB, Kang YJ, Kim SS, Kim CH, Kim SJ, et al. Hop extract produces antinociception by acting on opioid system in mice. Korean J Physiol Pharmacol 2012; 16(3): 187-92.
36. Kennedy DO, Little W, Haskell CF, Scholey AB. Anxiolytic effects of a combination of Melissa officinalis and Valeriana officinalis during laboratory induced stress. Phytother Res 2006; 20(2): 96-102.
37. Wahling C, Wegener T, Tschaikin M. Herbal triple combination: An effective alternative to benzodiazepines. Zeitschrift für Phytotherapie 2009; 30(2): 69-72.