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A novel approach of substitution therapy with inhalation of essential oil for the reduction of inhalant craving: A double-blinded randomized controlled trial

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ABSTRACT

Inhalants, which are neurotoxic central nervous system (CNS) suppressants, are frequently abused by young adults. Unlike other CNS depressants, including alcohol and opiates, no treatment is currently approved for inhalant dependence. In this report, a novel approach of substitution treatment for inhalant addiction was explored in a double-blinded, randomized, controlled crossover design to examine the effects of inhalation of essential oil and perfume on the reduction of cue-induced craving for inhalant in thirty-four Thai males with inhalant dependence. The craving response was measured by the modified version of Penn Alcohol Craving Score for Inhalants (PACS-inhalants). The participants (mean age ± SE = 27.9 ± 1.4) in this trial had used inhalant for 5.8 ± 1.1 years. Cravings could be induced in all participants by visual cues as assessed by ˆ50% increases in inhalant craving levels. Generalized estimating equations showed a significant suppressant effect of essential oil, but not perfume, on the craving response as compared with baseline cue-induced craving. Moreover, essential oil, but not perfume, had significant effects on physiological responses including decreasing pulse rate. It is concluded that inhaling essential oil as a substitution treatment for inhalant may be used as part of treatment programs for reducing inhalant craving.

1. Introduction

Inhalants, a class of neurotoxic hydrocarbon-based substances, are abused illegally worldwide by young adults and adolescents for recreation. Toluene, a volatile solvent found in glue and thinners, is the most common kind of inhalant being abused. Upon chronic sniffing, it may damage myelin sheaths and the white matter in the central nervous system (CNS) (Aydin et al., 2002; Lolin, 1989) and disrupt the glutamatergic (Bale et al., 2005; Beckley and Woodward, 2011; Chan et al., 2012; Hester et al., 2011; Wang et al., 2014; Win-Shwe et al., 2007) and gamma-aminobutyric acid (GABA) activity response (MacIver, 2009; O'Leary-Moore et al., 2007; Riegel and French, 1999) resulting in increased dopaminergic activity, a common pathway associated with addiction (Duncan and Lawrence, 2013).

Although it was believed that chronic use of inhalant does not produce withdrawal symptoms, a number of studies and reviews reported a range of inhalant withdrawal symptoms similar to those produced by withdrawal of other CNS suppressants (Kalayasiri and Maes, 2016; Perron et al., 2011, 2009). Symptoms of the inhalant craving response may be induced by external stimuli including picture cues of inhalant (Maneesang et al., 2012). This cue-induced inhalant craving involves several CNS biochemical pathways in different brain regions (Anton, 1999). Nevertheless, unlike other CNS suppressants, including alcohol and opiates, pharmacological treatment for withdrawal symptoms of or craving for inhalant is not available to date.

Treatments for abuse of addictive substances may be more efficient when using a same route of administration, namely sniffing or inhaling volatile chemicals when treating inhalant abuse. Patients may feel more convenient being treated using the same route of administration as the substance of abuse. Since the route of administration of inhalant is highly specific given the chemical property of inhalant, one pharmacological approach for studying therapeutic chemicals, which may reduce craving for inhalant, could focus on chemicals that can be inhaled.

Extracted oils from plants, namely essential oils, have been used to promote emotional well-being for more than 6000 years since ancient Egypt times. The volatile chemical oils extracted from leaf, fruit, flower or seed of plants, may affect emotions both in human and animal (Cavanagh and Wilkinson, 2002; Leelapornpisid, 2004; Ministry of Public Health of Thailand, 2007). Essential oil may reduce stress in individuals with intact smell sensation possibly through olfactory

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nerves located in the roof of nasal cavity, thereby signaling the chemical effects from the olfactory bulb to the limbic system, the brain area responsible for emotion and memory (Koulivand et al., 2013). Triggering these pathways may attenuate hyperautonomic nervous activity (Saeki, 2000; Sayorwan et al., 2012). The therapeutic use of essential oils has a number of documented therapeutic effects, including reducing fatigue symptoms following chemotherapy in breast cancer patients (Tumvijit, 2004), fatigue in HIV infected individuals (Hayee, 2008), insomnia in non-severe major depressive disorder or midlife women (Chien et al., 2012; Jariyapayuklert and Pratumsri, 2006), depressive symptoms and high blood pressure in the elderly (Muangnil, 2006), anxiety in pre-surgical patients (Ratapaibool, 2009) and stress in adolescents (Seo, 2009). Furthermore, essential oils may increase relaxation in intensive surgical care unit patients (Palakawong-na-Ayuthaya, 2012; Yammeesri, 2004). On the other hand, essential oils have no effect on alleviating subjective abdominal pain in women in labor (Smith et al., 2011), but may be used as an adjunctive pain control after cesarean section (Olapour et al., 2013). It is also important to note that different kinds of essential oils may produce different therapeutic effects, which may be attributed to different effects of the chemicals in essential oils (Ali et al., 2015). While synthetic perfumes may produce pleasant odors similar to plant essential oils, perfumes do not have therapeutic properties due to the lack of volatile oils.

Essential oils have also been investigated in the treatment of addictions. For example, essential oils were used to reduce alcohol withdrawal symptoms with an efficacy comparable to that of acupuncture (Kunz et al., 2007). Japanese researchers found that essential oils extracted from Matatabi induce euphoric-like effects in cats sniffing the plants by stimulating amygdala and hypothalamus (Katahira and Iwai, 1975; Sakan, 1967). Nevertheless, no studies examined the therapeutic effects of essential oils in patients with inhalant addictions.

Hence, this study was carried out to examine the therapeutic effects of essential oils reducing cue-induced inhalant craving – a strong desire to use inhalants after watching inhalant pictures. An essential oil extracted from the flower tip of the *Lavandula angustifolia* or lavender, a complex mixture of natural chemicals such as linalool and linalyl acetate (Shellie et al., 2002), was used. Lavender may reduce stress or agitation (Koulivand et al., 2013; Lin et al., 2007; Motomura et al., 2001) and insomnia (Chien et al., 2012; Lee and Lee, 2006; Lytle et al., 2014) and induce a feeling of relaxation (Sayorwan et al., 2012). Relaxation may reduce substance craving as observed in a study of behavioral treatment of cigarette craving (Limsanon and Kalayasiri, 2015). In a study investigating physiological, sensory, and affective responses after inhalation of essential oils, lavender altered retrospective pain experiences, which was hypothesized to be mediated through the pleasant sensory and affective stimuli of lavender oil (Gedney et al., 2004).

Thus this study was performed to examine whether craving for inhalant may be attenuated by lavender essential oil using perfume with lavender odor as control in a randomized controlled study. The primary hypothesis is that lavender may attenuate inhalant craving through pleasant affective responses after inhalation.

2. Materials and methods

2.1. Participants

Participants were thirty-four Thai-speaking males ˆ18 years old who were diagnosed with inhalant dependence. They were recruited by purposive sampling at the Substance Abuse Treatment Center, Central Thailand where they received psychosocial treatment according to the 1991 Rehabilitation Thai Law Act for substance abuse treatment. They participated in a double-blinded, randomized, controlled cross-over design study from July 2010 to November 2010. The diagnosis of inhalant dependence was made using the Diagnosis and Statistical Manual for Mental Disorders version IV (DSM-IV) using the Mini International Neuropsychiatric Interview (M.I.N.I. – lifetime, computerized Thai version). Participants with ability to smell were only included if they could correctly identify 3 out of 5 odors, namely fish sauce, lemon, onion, basil, and jasmine. Included were individuals with inducible picture-cues inhalant craving (see below) based on a 50% increase in craving score after cue exposure on the baseline day. We excluded individuals with a history of major psychiatric disorders, including psychotic and mood disorders, individuals with illicit substance dependence other than inhalant as diagnosed using M.I.N.I. and Section B (Medical History) of the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) and subjects with epilepsy, hypertension, or allergic reactions to essential oils or perfumes. Individuals who had a lifetime history of nicotine or alcohol dependence were not excluded. However cigarette and alcohol were strictly prohibited in the hospital and individuals with current nicotine or alcohol withdrawal symptoms were excluded. The study procedure has been approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University and the Ethics Committee of the Princess Mother National Institute of Drug Abuse Treatment, Thailand. ClinicalTrials.gov identifier: NCT03296943.

2.2. Measures

Craving was measured by the Penn Alcohol Craving Scale for Inhalants (PACS-inhalants) (Maneesang et al., 2012). The computerized Thai version comprises 5 questions scored from 0 to 6 for each question in Likert scales and the Visual Analog Scale (VAS) scaled from 0 (not at all) to 10 (most ever). VAS scores were also used to measure a range of subjective experiences including high, stimulated, anxious, restless, paranoia, hungry, tongue-tied, and bad feelings (Limsanon and Kalayasiri, 2015). Baseline cue-induced craving was assessed on the screening/test day as the ability to respond to inhalant picture-cues for craving. Details of the cue-induced craving procedure on the screening day were described in details elsewhere (Maneesang et al., 2012). In brief, the cue-induced craving was tested by exposing individuals with a set of 12 pictures for one-minute (e.g., 5 s display per picture) every five minutes for three sets in total followed by another three sets of neutral/relaxing pictures of nature (e.g., forest, water fall, river, and ocean). Craving and other substance-related subjective feelings and objective measures including systolic and diastolic blood pressure and pulse rate were measured 5 min before the cue display and after exposure to each set of inhalant and neutral pictures every five minutes. The procedure of picture display and the subjective and objective measurements on the two days of receiving interventions with either essential oil or perfume were identical to the baseline day as shown in Fig. 1.

2.3. Interventions

Essential oil is prepared from the product of Thailand with manufacture standard ID 1087/2548 by Thailand Ministry of Industry with 0.67% concentration. Essential oil is extracted by a cold compressed method from the *Lavandula angustifolia* (lavender) grown in Australia. The product had weak acidity at pH = 5.6. Perfume is the synthetic perfume of lavender flavor without essential oil. The containers for essential oil and perfume, are identical dark-glass tubes with a roll-on-cap on top and double-covered with a plain cap on each tube. The participants were randomly allocated to essential oil first or perfume first after passing the screening criteria by using ballot drawing prepared by a research assistant who assigned participants to intervention at each stage. Each participant received one container. Then all subjects were crossed over to receive the other treatment two days later without the knowledge of the treatment they received. One of the investigators (W.M.), a registered nurse with a master degree in mental health, was trained to carry out the intervention. W.M. was blinded to the intervention and enrolled participants, delivered the treatment substance and assessed intervention fidelity. Moreover, W.M. attended all

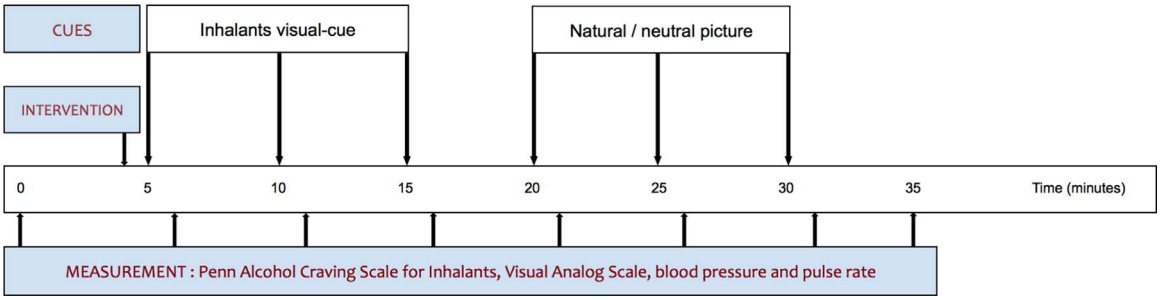

Fig. 1. Shows diagram of the cue-induced craving paradigm presenting timeline with measurement and intervention with essential oil inhalation or perfume inhalation on intervention days and baseline (no-intervention) day. The cue-induced craving was tested by exposing individuals with a set of 12 pictures for one-minute (e.g., 5 s display per picture) every five minutes for three sets in total followed by another three sets of neutral/relaxing pictures of nature (e.g., forest, water fall, river, and ocean). Craving and other substance-related subjective feelings and objective measures including systolic and diastolic blood pressure and pulse rate were measured 5 min before the cue display and after exposure to each sets of inhalant and neutral pictures every five minutes.

interventions to ensure participants' attention to the protocol. To inhale the essential oil and perfume in an air-conditioned room, the container was flipped over to soak the roll-on cap that was then rolled-on circularly at the right mid-palm of the subject at 2 cm in diameter for 5 cycles (~ 0.02 milliliter). The subjects were asked to rub their palms together for exactly 10 times immediately after the application, then closed their nose and mouth with two hands and inhaled the chemicals for 5 s then exhaled. The inhalation was set for three times in total. Right after the inhalation, the inhalant cues were displayed. The subjective and objective measurements were performed before the inhalation (0-min;) and during the display of each set of inhalant cues (5-, 10-, 15-min) as described above.

2.4. Analysis

Normality of data distributions were checked using the Kolmogorov-Smirnov test and by visual inspection. Craving, other subjective feelings and vital-sign measurements prior and during the visual-cue exposure were analyzed using Generalized Estimating Equations (GEE) to examine the effects of essential oil and perfume comparing to baseline day. Data at 0-min and age were entered as covariates. Pair-wise post–hoc analysis were employed to compare between the three groups. Data with normal distribution were analyzed with a linear model and those without normal distribution were analyzed using an ordinal probit model in the GEE analysis.

3. Results

Fig. 2 displays the consort flow diagram showing the progress of the participants through the double-blinded randomized trial. Of 34 inhalant-dependent individuals, all (100%) were male and 32 (94.1%) had inhaled glue and 2 (5.9%) had inhaled thinner with an average duration of 5.8 ± 1.1 years. The mean age ± SE of the subjects was 27.9 ± 1.4 years. Twenty-two and 20 subjects had a lifetime history of

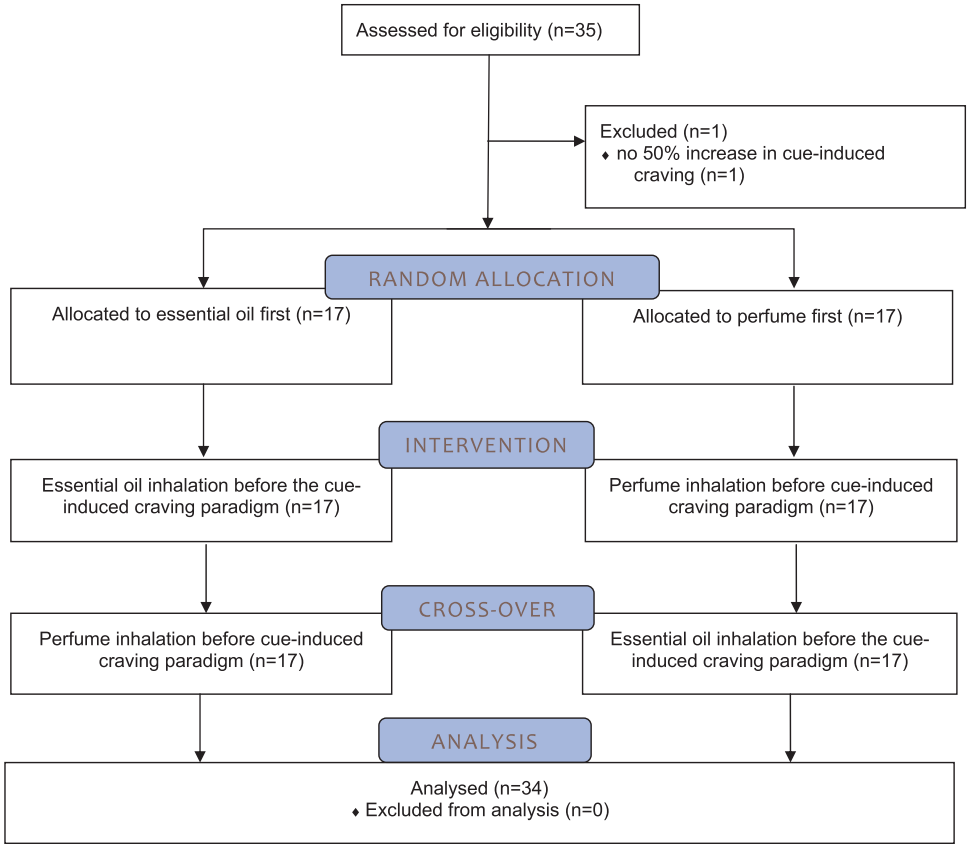

Fig. 2. Consort flow diagram of the study design showing participants receiving essential oil first (n = 17) and perfume first (n = 17). One inhalant user was excluded during eligibility screening because this patient did not show a 50% increase in inhalant craving after exposing to inhalant picture-cues. None of the participants were excluded after the recruitment.

Table 1
Craving for inhalant, other subjective feelings, and vital signs of individuals with inhalant dependence participating in the cue-induced paradigm on the baseline day and the days receiving treatments.

	Baseline n = 34 Mean ± SD	Perfume n = 34 Mean ± SD	Essential Oil n = 34 Mean ± SD
Craving (PACS-Inhalants)[a]	7.6 ± 0.9	5.7 ± 0.4	5.2 ± 0.9
Other feelings (VAS)[b]			
Craving	2.3 ± 0.4	1.8 ± 0.4	1.3 ± 0.3
Stimulation	2.3 ± 0.4	1.8 ± 0.4	1.3 ± 0.4
Anxiety	1.9 ± 0.4	1.3 ± 0.3	1.1 ± 0.3
Hungry	1.8 ± 0.4	1.4 ± 0.3	1.2 ± 0.4
High	2.1 ± 0.4	2.0 ± 0.4	1.2 ± 0.3
Paranoid	1.5 ± 0.4	1.4 ± 0.3	1.3 ± 0.4
Tongue-tied	2.0 ± 0.4	1.7 ± 0.4	1.5 ± 0.4
Feeling bad	2.0 ± 0.4	1.7 ± 0.4	1.4 ± 0.4
Restlessness	1.8 ± 0.3	1.5 ± 0.3	1.0 ± 0.2
Vital signs			
Systolic BP[c]	116.5 ± 2.3	113.8 ± 2.5	113.5 ± 1.9
Diastolic BP	67.4 ± 1.7	65.7 ± 1.7	66.6 ± 1.4
Pulse rate	75.2 ± 1.8	74.8 ± 1.8	74.2 ± 1.7

Scores were averaged from all time points at 0-, 5-, 10-, 15-, 20-, 25-, 30-, and 35-min when inhalant visual-cue and natural/neutral picture were presented.
[a] Penn Alcohol Craving Scale – Inhalants (PACS-Inhalants), full score = 30.
[b] Visual Analog Scale (VAS), full score = 10.
[c] Blood pressure (BP; mmHg).

nicotine (64.7%) and alcohol (58.8%) dependence, respectively. Some participants had a lifetime, but not current, history of other illicit substance use, namely methamphetamine (n = 20; 58.8%), cannabis (n = 13; 38.2%) and opium (n = 5; 14.7%).

Table 1 shows average scores on overall craving for inhalant, other feelings and vital signs across three days of the study (e.g., baseline, perfume day, essential oil day). Scores at baseline day were higher than those on the other two intervention days for all studied variables. Likewise, average scores on perfume day were higher than those on essential oil day for almost all variables, except for diastolic blood pressure.

Fig. 3 shows the responses on craving at pre-test (0-min) and cue pictures at 5-, 10-, and 15-min across the three days of the study. GEE analysis showed significant effects of treatment (Wald Chi-square$_2$ = 11.381, p = 0.003) but not time or treatment X time interaction (Ps > 0.05) on inhalant craving. Post-hoc analysis showed a significant effect of essential oil (Wald Chi-square$_1$ = 7.554, p = 0.006) and a trend toward a significant effect of perfume (Wald$_1$ = 3.383, p = 0.066) as compared to baseline intervention. However, no significant time effect or interactions time X essential oil and perfume on the inhalant craving response to picture cues were observed (Ps > 0.05) (Fig. 2).

Fig. 4 shows the VAS scores during exposure to visual cues for inhalant. Significant effects of time were observed on tongue-tied scores (Wald$_1$ = 7.334, p = 0.007) and significant effects of treatment X time were observed on hungry (Wald$_2$ = 6.631, p = 0.036) and feeling bad (Wald$_2$ = 6.621, p = 0.036). Pair-wise post-hoc analysis showed significant effects of perfume X time on hungry scores (Wald$_1$ = 6.313, p = 0.012) and essential oil X time on feeling bad scores (Wald$_1$ = 6.617, p = 0.010) as compared to no intervention. No differences of these measures were observed between essential oil and perfume.

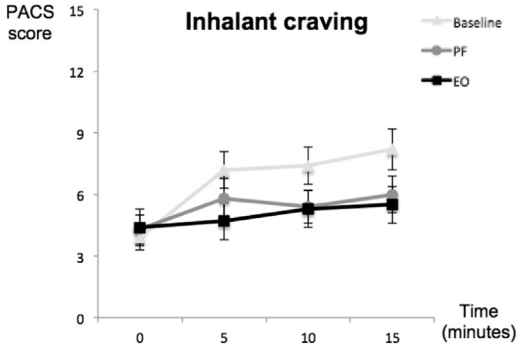

Fig. 3. Shows significant effects of treatment on inhalant craving as measured by PACS-Inhalants (p = 0.003) but not time or treatment X time interaction (Generalized Estimating Equations). Post-hoc analysis showed a significant effect of essential oil (EO) (p = 0.006) and a trend toward a significant effect of perfume (PF) (p = 0.066) as compared to baseline intervention.

None of other VAS scores including feeling stimulated, anxious, paranoia, feeling high, restlessness, and VAS craving response nor on physiological measures including diastolic BP and pulse rate were affected by treatment, time, or treatment X time interactions (Ps > 0.05), though a nearly significant effects of treatment (Wald$_2$ = 5.439, p = 0.066) and treatment X time interaction (Wald$_1$ = 5.959, p = 0.051) on pulse rate were observed. Post-hoc analysis showed a significant effect of essential oil (Wald$_1$ = 4.592, p = 0.032) and essential oil X time interaction (Wald$_1$ = 5.839, p = 0.016) on pulse rate as compared to perfume, but not baseline (Ps > 0.05). Although the VAS craving response was not affected by the treatment as the main effect, post-hoc analysis comparing between essential oil and perfume on the VAS feelings showed a trend significant effect of essential oil on VAS craving (Wald$_1$ = 3.368, p = 0.066).

In addition, a significant effect of essential oil treatment X time interaction on systolic blood pressure as compared to no intervention at baseline (Wald$_1$ = 5.321, p = 0.021) and a trend effect of the interaction as compared to perfume intervention (Wald$_1$ = 3.572, p = 0.059) were observed. No immediate harms or unintended outcomes were observed in both interventions.

4. Discussion

A randomized-controlled cross-over design was used to investigate the effects of a new approach for inhalant dependency treatment in the reduction of cue-induced inhalant craving. The increased inhalant craving after exposure to visual-cues could be attenuated by inhaling vapor of essential oil when compared to the non-treatment at baseline, whereas perfume treatment showed only a trend toward significance. Furthermore, essential oil significantly reduced objective physiological measurements including pulse rate and systolic blood pressure when compared to the no-treatment condition. The reduction in pulse rate was significantly greater in essential oil than in perfume treated condition, whilst there was a trend towards greater reductions in systolic

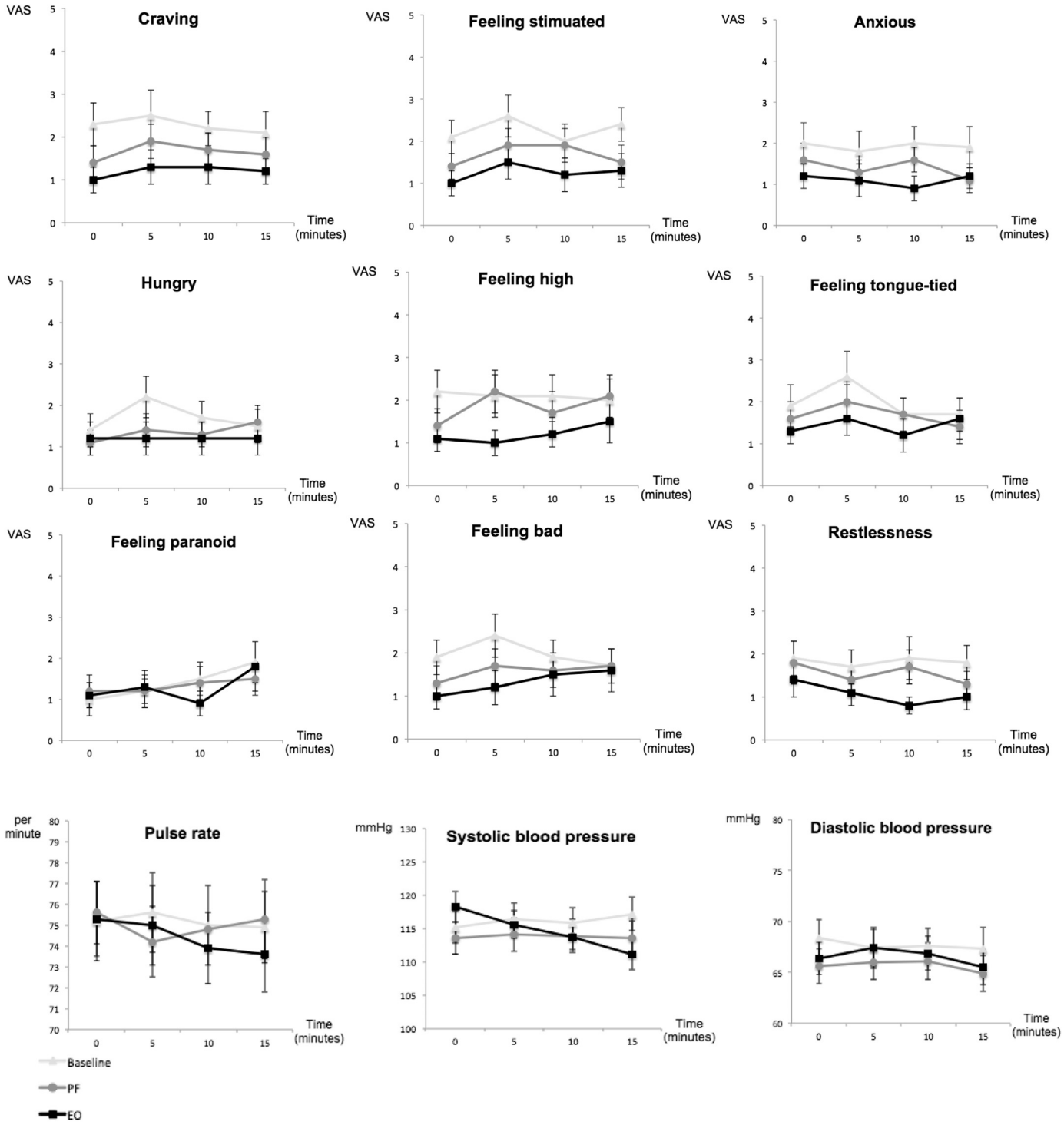

Fig. 4. Shows the treatment effects on VAS scores and systolic and diastolic blood pressure and pulse rate. Significant effects of perfume (PF) X time on hungry scores ($p = 0.012$) and essential oil (EO) X time on feeling bad scores ($p = 0.010$) as compared to no intervention were observed. The reduction in pulse rate was significantly greater in EO than in PF treated condition ($p = 0.016$).

blood pressure during essential oil than perfume treatment. Moreover, essential oil significantly attenuated VAS scores of feeling bad while perfume had a significant effect on feeling hungry as compared with the no-treatment condition. On the other hand, essential oil did not affect other VAS scores including feeling stimulated, anxious, paranoia, restless, high, and craving and other physiological responses including diastolic blood pressure.

We reported previously on the effects of inhalant visual-cues on craving and objective physiological responses (Maneesang et al., 2012). The significant effect of inhalant visual-cues on craving were not observed in the current analysis, partly due to exclusion of the baseline (0-min) data that was entered as a covariate. The non significant effect of visual-cues on physiological responses, in the current study was in agreement with results of our previous report (Maneesang et al., 2012). Nevertheless, our findings are not in agreement with reports on cue-induced physiological changes by other substances (Childress et al., 1999; Culbertson et al., 2010; Ren et al., 2009). These differences between essential oil and other substances may be explained by findings

that inhalant may produce less severe dependence than hard drugs, including opioids, methamphetamine and cocaine (American Psychiatric Association, 2000, 2013; Perron et al., 2011, 2009). In addition, the inhalant visual-cues used in our study did not induce other unpleasant feelings which are frequently observed with craving (e.g., anxious and restlessness), suggesting that craving for inhalant may be a milder phenomenon. In contrast, tongue-tied feelings appear to be a phenomenon that could be induced by exposure to sets of visual cues. However, given the low tongue-tied feeling levels, namely VAS scores < 3, these effects are clinically less relevant.

Thus, while essential oil treatment significantly reduced craving, essential oil had also some effects on objective measures, namely systolic blood pressure and pulse rate, and subjective measures, including feeling bad. The effect of essential oil reducing pulse rate and systolic blood pressure may be associated with craving reduction and mediated through a decrease in sympathetic autonomic nervous response or enhancement of the parasympathetic response (Sayorwan et al., 2012). The attenuating effect of essential oil on unpleasant feelings or stress could mediate the effect of this compound on the inhalant craving response. Moreover, essential oil may increase relaxation and alleviate unpleasant feelings/symptoms in a host of conditions (Hayee, 2008; Jariyapayuklert and Pratumsri, 2006; Koulivand et al., 2013; Muangnil, 2006; Ratapaibool, 2009; Saeki, 2000; Sayorwan et al., 2012; Seo, 2009; Tumvijit, 2004). Thus, the calming and soothing effects of essential oil may explain in part its effects reducing craving responses as observed with other substances (Limsanon and Kalayasiri, 2015; Tang et al., 2016).

Our study does not fully agree with the theory that synthetic perfume is devoid of the effects of the volatile chemicals in essential oil, which reduce stress and exert other beneficial therapeutic effects (Ali et al., 2015). Indeed, the current study showed that perfume may have some effects on craving although less significant than essential oil. The substitution of inhalant by essential oil or perfume using the same route of administration and the distraction from cues by the essential oil or perfume odors may explain these effects. Nevertheless, the stronger effects of essential oil reducing craving and pulse rate and some VAS scores as compared with perfume indicate that essential oil chemicals may have effects beyond the effects of odor alone. Future research should examine the chemicals in essential oil that may exert therapeutic activities on inhalant craving.

Several limitations should be discussed. Firstly, no toxicology tests were performed to confirm whether inhalant users were abstaining from using the drugs. The type/brand of glue and chemical content used by participants were not collected. In addition, although we exclude individuals with current illicit use, we did not exclude participants who currently had legal substance dependence. Therefore, craving could be confounded by the abstinence of other substances that correlated with inhalant use. Secondly, we did not monitor possible side effects from essential oil or perfume although, in theory, allergies to essential oil may occur. Likewise, we did not employ any additional measure to control the amount and concentration of the essential oil other than the assumptions that the same amount of essential oil was applied on each individual's palm by following a strict protocol of solution application and the solution was well mixed with stable concentration over each container in each experiment. Thirdly, the non-treatment condition was not randomly allocated but was fixed as the first condition and therefore sequence effects may take place. Nevertheless, our results were adjusted for the baseline values (before administration of essential oil and perfume) on the two treatment days thereby controlling for baseline values and thus possible bias by sequence effects.

In conclusion, inhalation of volatile essential oil chemicals may be used to reduce inhalant craving at least in a clinical setting. Future research should examine the effects of essential oil administration in non-clinical settings and the long term outcome of essential oil treatments including therapeutic and side effects.

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Authors contribution

Rasmon Kalayasiri for designing the study and instruments, data analysis, and writing manuscript

Wanjaree Maneesang for data collection and data analysis

Michael M. Maes for editing the manuscript extensively

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Conflict of interest

None.

References

Ali, B., Al-Wabel, N.A., Shams, S., Ahamad, A., Khan, S.A., Anwar, F., 2015. Essential oils used in aromatherapy: a systemic review. Asian Pac. J. Trop. Biomed. 5 (8), 601–611.
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, D.C.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5). American Psychiatric Publishing, Arlington, VA.
Anton, R.F., 1999. What is craving? Models and implications for treatment. Alcohol Res Health 23 (3), 165–173.
Aydin, K., Sencer, S., Demir, T., Ogel, K., Tunaci, A., Minareci, O., 2002. Cranial MR findings in chronic toluene abuse by inhalation. AJNR Am. J. Neuroradiol. 23 (7), 1173–1179.
Bale, A.S., Tu, Y., Carpenter-Hyland, E.P., Chandler, L.J., Woodward, J.J., 2005. Alterations in glutamatergic and gabaergic ion channel activity in hippocampal neurons following exposure to the abused inhalant toluene. Neuroscience 130 (1), 197–206.
Beckley, J.T., Woodward, J.J., 2011. The abused inhalant toluene differentially modulates excitatory and inhibitory synaptic transmission in deep-layer neurons of the medial prefrontal cortex. Neuropsychopharmacology 36 (7), 1531–1542.
Cavanagh, H.M., Wilkinson, J.M., 2002. Biological activities of lavender essential oil. Phytother. Res. 16 (4), 301–308.
Chan, M.H., Lee, C.C., Lin, B.F., Wu, C.Y., Chen, H.H., 2012. Metabotropic glutamate receptor 5 modulates behavioral and hypothermic responses to toluene in rats. Pharmacol. Biochem. Behav. 103 (2), 418–424.
Chien, L.W., Cheng, S.L., Liu, C.F., 2012. The effect of lavender aromatherapy on autonomic nervous system in midlife women with insomnia. Evid. Based Complement. Altern. Med 2012, 740813.
Childress, A.R., Mozley, P.D., McElgin, W., Fitzgerald, J., Reivich, M., O'Brien, C.P., 1999. Limbic activation during cue-induced cocaine craving. Am. J. Psychiatry 156 (1), 11–18.
Culbertson, C., Nicolas, S., Zaharovits, I., London, E.D., De La Garza 2nd, R., Brody, A.L., Newton, T.F., 2010. Methamphetamine craving induced in an online virtual reality environment. Pharmacol. Biochem. Behav. 96 (4), 454–460.
Duncan, J.R., Lawrence, A.J., 2013. Conventional concepts and new perspectives for understanding the addictive properties of inhalants. J. Pharmacol. Sci. 122 (4), 237–243.
Gedney, J.J., Glover, T.L., Fillingim, R.B., 2004. Sensory and affective pain discrimination after inhalation of essential oils. Psychosom. Med. 66 (4), 599–606.
Hayee, F., 2008. The Effect of Symptom Management Combining Aromatherapy Massage Program on Fatigue Among HIV-Infected Persons, Nursing. Prince of Songkla University, Songkla.
Hester, S.D., Johnstone, A.F., Boyes, W.K., Bushnell, P.J., Shafer, T.J., 2011. Acute toluene exposure alters expression of genes in the central nervous system associated

with synaptic structure and function. Neurotoxicol Teratol. 33 (5), 521–529.
Jariyapayuklert, K., Pratumsri, V., 2006. Effects of lavender essential oil on insomnic patients with major depressive disorder. Public Health J. Burapha Univ. 1 (1), 47–51.
Kalayasiri, R., Maes, M., 2016. Addiction to, neurobiology of, and genetics of inhalants. In: Preedy, V.R. (Ed.), Neuropathology of Drug Addictions and Substance Misuse. Academic Press, London, pp. 958–962.
Katahira, K., Iwai, E., 1975. Effect of unilateral lesion of amygdala on unmanifested response to Matatabi (Actinidia polygama) in cats. Tohoku J. Exp. Med. 115 (2), 137–143.
Koulivand, P.H., Khaleghi Ghadiri, M., Gorji, A., 2013. Lavender and the nervous system. Evid. Based Complement. Altern. Med. 2013, 681304.
Kunz, S., Schulz, M., Lewitzky, M., Driessen, M., Rau, H., 2007. Ear acupuncture for alcohol withdrawal in comparison with aromatherapy: a randomized-controlled trial. Alcohol Clin. Exp. Res. 31 (3), 436–442.
Lee, I.S., Lee, G.J., 2006. Effects of lavender aromatherapy on insomnia and depression in women college students. Taehan Kanho Hakhoe Chi 36 (1), 136–143.
Leelapornpisid, P., 2004. Aromatherapy. O.S. Printing House, Bangkok.
Limsanon, T., Kalayasiri, R., 2015. Preliminary effects of progressive muscle relaxation on cigarette craving and withdrawal symptoms in experienced smokers in acute cigarette abstinence: a randomized controlled trial. Behav. Ther. 46 (2), 166–176.
Lin, P.W., Chan, W.C., Ng, B.F., Lam, L.C., 2007. Efficacy of aromatherapy (Lavandula angustifolia) as an intervention for agitated behaviours in Chinese older persons with dementia: a cross-over randomized trial. Int. J. Geriatr. Psychiatry 22 (5), 405–410.
Lolin, Y., 1989. Chronic neurological toxicity associated with exposure to volatile substances. Hum. Toxicol. 8 (4), 293–300.
Lytle, J., Mwatha, C., Davis, K.K., 2014. Effect of lavender aromatherapy on vital signs and perceived quality of sleep in the intermediate care unit: a pilot study. Am. J. Crit. Care 23 (1), 24–29.
MacIver, M.B., 2009. Abused inhalants enhance GABA-mediated synaptic inhibition. Neuropsychopharmacology 34 (10), 2296–2304.
Maneesang, W., Verachai, V., Kalayasiri, R., 2012. Effects of video cues on inhalants craving in individuals receiving inhalants substance-dependency treatment. Chula Med. J. 56 (2), 147–161.
Ministry of Public Health of Thailand, 2007. Aromatherapy Textbook. Veteran Publishing House, Bangkok.
Motomura, N., Sakurai, A., Yotsuya, Y., 2001. Reduction of mental stress with lavender odorant. Percept. Mot. Skills 93 (3), 713–718.
Muangnil, P., 2006. Effect of Aroma Oil Massage on Depression State in Older Adults Nursing. Mahidol University, Bangkok.
O'Leary-Moore, S.K., Galloway, M.P., McMechan, A.P., Hannigan, J.H., Bowen, S.E., 2007. Region-dependent alterations in glutamate and GABA measured by high-resolution magnetic resonance spectroscopy following acute binge inhalation of toluene in juvenile rats. Neurotoxicol. Teratol. 29 (4), 466–475.
Olapour, A., Behaeen, K., Akhondzadeh, R., Soltani, F., Al Sadat Razavi, F., Bekhradi, R., 2013. The effect of inhalation of aromatherapy blend containing lavender essential oil on cesarean postoperative pain. Anesth. Pain. Med. 3 (1), 203–207.
Palakawong-na-Ayuthaya, W., 2012. Effectiveness of aromatherapy massage on relaxation among patients in surgical intensive care unit of Bhumibol Adulyadej hospital, Directorate of medical services, Royal Thai air force. R. Thai Air Force Med. Gaz. 58 (2), 66–71.
Perron, B.E., Glass, J.E., Ahmedani, B.K., Vaughn, M.G., Roberts, D.E., Wu, L.T., 2011. The prevalence and clinical significance of inhalant withdrawal symptoms among a national sample. Subst. Abus. Rehabil. 2011 (2), 69–76.
Perron, B.E., Howard, M.O., Vaughn, M.G., Jarman, C.N., 2009. Inhalant withdrawal as a clinically significant feature of inhalant dependence disorder. Med. Hypotheses 73 (6), 935–937.
Ratapaibool, L., 2009. The Effect of Pre-Operative Preparatory Program and Aromatherapy on Patients, Anxiety During Pre-Operative and Intra-Operative Phase in Patients Undergoing Ambulatory Surgery, Nursing. Prince of Songkla University, Songkla.
Ren, Z.Y., Zhang, X.L., Liu, Y., Zhao, L.Y., Shi, J., Bao, Y., Zhang, X.Y., Kosten, T.R., Lu, L., 2009. Diurnal variation in cue-induced responses among protracted abstinent heroin users. Pharmacol. Biochem. Behav. 91 (3), 468–472.
Riegel, A.C., French, E.D., 1999. The susceptibility of rat non-dopamine ventral tegmental neurones to inhibition during toluene exposure. Pharmacol. Toxicol. 85 (1), 44–46.
Saeki, Y., 2000. The effect of foot-bath with or without the essential oil of lavender on the autonomic nervous system: a randomized trial. Complement. Ther. Med. 8 (1), 2–7.
Sakan, T., 1967. Matatabi (Actinidia polygama Miq.)–isolation and structure of its biologically active components. Tanpakushitsu Kakusan Koso 12 (1), 2–9.
Sayorwan, W., Siripornpanich, V., Piriyapunyaporn, T., Hongratanaworakit, T., Kotchabhakdi, N., Ruangrungsi, N., 2012. The effects of lavender oil inhalation on emotional states, autonomic nervous system, and brain electrical activity. J. Med. Assoc. Thai 95 (4), 598–606.
Seo, J.Y., 2009. The effects of aromatherapy on stress and stress responses in adolescents. J. Korean Acad. Nurs. 39 (3), 357–365.
Shellie, R., Mondello, L., Marriott, P., Dugo, G., 2002. Characterisation of lavender essential oils by using gas chromatography-mass spectrometry with correlation of linear retention indices and comparison with comprehensive two-dimensional gas chromatography. J. Chromatogr. A 970 (1–2), 225–234.
Smith, C.A., Collins, C.T., Crowther, C.A., 2011. Aromatherapy for pain management in labour. Cochrane Database Syst. Rev. (7), CD009215.
Tang, Y.Y., Tang, R., Posner, M.I., 2016. Mindfulness meditation improves emotion regulation and reduces drug abuse. Drug Alcohol Depend. 163 (Suppl. 1), S13–S18.
Tumvijit, S., 2004. The Effect of Symptom Management With Aromatherapy Massage Program on Fatigue in Breast Cancer Patients After Mastectomy Undergoing Chemotherapy, Nursing. Chulalongkorn University, Bangkok.
Wang, F., Li, C., Liu, W., Jin, Y., 2014. Potential mechanisms of neurobehavioral disturbances in mice caused by sub-chronic exposure to low-dose VOCs. Inhal. Toxicol. 26 (4), 250–258.
Win-Shwe, T.T., Mitsushima, D., Nakajima, D., Ahmed, S., Yamamoto, S., Tsukahara, S., Kakeyama, M., Goto, S., Fujimaki, H., 2007. Toluene induces rapid and reversible rise of hippocampal glutamate and taurine neurotransmitter levels in mice. Toxicol. Lett. 168 (1), 75–82.
Yammeesri, W., 2004. Effect of Aromatherapy on Relaxation Among Patients in Surgical Critical Care Unit, Nursing. Chiang Mai University, Chiang Mai.